Review

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JN.1 variant in enduring COVID-19 pandemic: is it a variety of interest (VoI) or variety of concern (VoC)?

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Abstract: The emergence of the SARS-CoV-2 Omicron variant, classified as a Variant of Concern (VoC) in November 2021, marked a significant shift in the COVID-19 landscape. This study investigates the subsequent development of a novel Omicron sublineage, JN.1, which displays distinctive mutations in the spike protein. The study delves into the phylogenetic differences between these variants and their potential implications. A comprehensive analysis of the genomic profiles and mutation patterns of JN.1 and BA.2.86 was conducted, utilizing SARS-CoV-2 database. The study explores the unique mutations, such as S:L455S in JN.1, associated with increased transmissibility and immune escape. Furthermore, a comparison with prevalent strains like XBB.1.5 and HV.1 highlights the substantial genetic divergence of JN.1. JN.1, first detected in August 2023, exhibits a notable spike protein mutation profile, including the reappearance of earlier variants' mutations (E484K and P681R). The variant's increased transmissibility and immune evasion potential are attributed to specific spike protein mutations like R21T, S50L, V127F, R158G, and others. The study also explores the distribution and prevalence of JN.1 globally, with a focus on the rising cases in India. JN.1 poses a unique challenge as one of the most immune-evading variants, with potential implications for COVID-19 transmission. The study emphasizes the importance of monitoring and understanding emerging variants, especially those with distinct spike protein mutations. The observed cases in India highlight the need for vigilance and prompt public health responses. As JN.1 continues to evolve, ongoing surveillance, vaccination strategies, and adherence to preventive measures are crucial to mitigating its potential impact on global public health.

Keywords: COVID-19; omicron variant; JN.1 variant; variety of interest (VOI); variety of concern (VOC)

Background

Although severe acute respiratory syndrome-associated SARS-CoV2, the original coronavirus, was the source of COVID-19 when it first appeared in Wuhan, China. Early in 2020, there was a global outbreak of cases that expanded quickly, leading to an epidemic that quickly spread and turned into a pandemic. This rocked the world's healthcare system. Before this month, or between November and December of 2021, the delta version of SARS-CoV-2 ruled supreme until the appearance of a newer variant, the Omicron of SARS-CoV-2. The advent of the alpha, beta, and delta variants of SARS-CoV-2 were linked to new waves of infections, sometimes throughout the entire world. There were 13 mutations in Delta. Nine of them are found in the spike protein, the protrusion on the virus' surface that facilitates its attachment to human cells. In particular, two have been identified in a molecular hook, called the "receptor-binding domain". Monstrous mutations gave rise to Omicron. 10 mutations are found in the receptor-binding domain and at least 32 in the spike protein. It was classified as a COVID-19 variation of concern (VoC) on November 26, 2021 by the World Health Organization (WHO) [1]. The omicron version has also been revealed to have structural
mutations in antibody binding locations, which could be used to evade the body’s potential immune reaction. The other modifications and their potential effects on the virus’s behavior are yet mostly unknown. Omicron COVID-19 strain following the identification of patients exhibiting distinct symptoms from those observed in the Delta form. The new omicron variant has more mutations than the prevailing uncontrolled delta virus. This makes the newer variant more transmissible [2]. Compared to the current rampant delta virus, the new omicron form has more mutations. This increases the newer variant’s transmissibility and improves its ability to elude the several vaccinations that are currently widely accessible [3]. These general increases in the percentage changes in COVID-19 reported cases reported in a single day can be interpreted as either the start of the third wave or as a more recent rise in cases with omicron variants [4, 5] (Figures 1–3).

First discovered in August 2023, the SARS-CoV-2 BA.2.86 lineage differs phylogenetically from the Omicron XBB lineages of SARS-CoV-2 that are presently in circulation, such as EG.5.1 and HK.3. In contrast to BA.2 and XBB, BA.2.86 has over 30 mutations in the spike (S) protein, suggesting a significant likelihood of immune evasion [6].

JN1 (BA.2.86.1.1)

After evolving from BA.2.86 commonly known as “Pirola”, BA.2.86 gave rise to JN1 (BA.2.86.1.1) which is another descendant of Omicron, which has appeared in late 2023. S:L455S and three mutations in non-S proteins are present in JN1. A characteristic mutation of JN1 is S:L455S [7]. It has been demonstrated lately that HK.3 and other “FLip” variations carry S:L455F, which increases transmissibility and immune escape capacity relative to the ancestral EG.5.1 variant [8, 9].

Mutations

A recently discovered COVID-19 variation shows how quickly the SARS-CoV-2 virus may evolve. On August 25, 2023, the JN.1 variety of SARS-CoV-2 emerged, first in Luxembourg and then in England, Iceland, France, and the United States. As of this writing, there are 91 instances of JN.1 in the GISAID SARS-CoV-2 database, indicating that potentially hundreds
or even thousands of people may have been infected with the variant as sequencing efforts have essentially stopped [7, 10].

The most fascinating aspect about JN.1 and the reason we think there should be some worry is how different it is from the two most common viruses in use now, XBB.1.5 and HV.1. The most recent vaccination boosters in the US are directed against the XBB.1.5 variant. The majority of new varieties are descended from this virus. HV.1 is a relatively new version that differs from XBB.1.5 in a few ways but is essentially the same.

In HV.1 compared to XBB.1.5, there are 10 additional unique mutations, or a difference of around 12%, which can be used to assess the departure of JN.1 from these viruses. Compared to XBB.1.5, JN.1 has 41 more distinct mutations. The spike protein exhibits the majority of JN.1’s alterations, which are probably related to rises in immune evasion and infectivity [7]. Coronavirus get their name from the projecting oligomers of spike glycoprotein (S) that surround the virus and form a coronal fringe. The coronavirus genome is nonsegmented, single-stranded, and RNA in the positive sense. Coronaviruses have been reported to exhibit mutated and recombined behavior, producing respiratory, intestinal, hepatic, and neurologic disorders, resulting in a wide range of sickness and symptoms [11].

We have previously observed several variants of concern, including E484K and P681R, which were initially discovered in the Alpha and Beta variants of SARS-CoV-2 in early 2021. Several of these mutations are present in spike protein variants. It is unknown why those mutations stopped being found in the Omicron family of variations, but it is remarkable that they have returned in JN.1.

The uniqueness of some mutations in the spike protein, rather than the resurfacing of prior variants, is what draws our attention to JN.1. From a collection of more than 16 million samples collected during the pandemic, just a few thousand sequences have been performed on several of these mutations. None, nevertheless, are exclusive to JN.1 [7].

Mutations like R21T, S50L, V127F, R158G, and others may enhance viral entry efficiency and immunological escape.
from antibodies by installing N-glycosylation sites in the N-terminal domain, which is involved in virus entry post-infection.

We find a comparable phenomenon in the receptor-binding domain. Together with other uncommon variants, V445H, S450D, and L452W have all been sequenced fewer than two thousand times. These mutations may all contribute to an increase in ACE2 binding affinity or a decrease in antibody binding effectiveness [3, 7].

What is the difference between VoI and VoC?

The term “variant under monitoring” (VUM) notifies public health authorities to the possibility that a SARS-CoV-2 variation has to be monitored and treated with priority. This category’s primary goal is to determine whether, in comparison to other circulating variants, this variant (and those closely related to it) may represent an extra threat to global public health [12].

The term “variant of interest” (VOI) refers to a variation of SARS-CoV-2 that has modifications that are known to alter the virus’s behavior or its effects on human health. This can include things like how readily it can be discovered or treated, how easily it can spread, and its capacity to cause major sickness. When compared to other circulating variants, a VOI may also be recognized due to its greater capacity for dissemination, indicating a possible developing risk to worldwide public health.

A SARS-CoV-2 variant that satisfies the above description of a variant of interest (VOI) and, when compared to other variants, at least one of the following criteria is met is referred to as a Variant of Concern (VOC):

- It may result in a negative shift in the severity of the illness.
- There is a marked decline in the efficacy of currently available vaccines in preventing serious disease; this can have a substantial impact on health systems’ capacity to treat patients with COVID-19 or other illnesses and necessitate large-scale public health interventions.

Signs and symptoms

Compared to other circulating variations of SARS-CoV-2, the JN.1 variant is more immune system evading and more easily transmissible [9]. Currently, this strain is found in numerous nations, including the USA, China, Singapore, and India. As of right now, there is no proof that JN.1 causes more severe illness than other virus strains. It can spread more easily and cause mild to moderate illness. Symptoms that are common to those infected with this kind of infection include fever, runny nose, sore throat, and headaches [13]. Thrombosis has been a critical manifestation in severe COVID-19 infection [14]. One significant indicator of the JN.1 variation is extreme tiredness. This tiredness goes beyond the usual tiredness experienced by COVID-19 individuals and is characterized by extreme exhaustion and muscle weakness. The majority of patients have moderate upper respiratory symptoms, which usually fade away in four to five days, however this variant JN.1 form is distinguished by specific features [15].

Indian case scenario

The addition of 412 fresh COVID-19 cases took India’s active cases tally to 4,093, Health Ministry stated on Wednesday (27th Dec, 2023) [16]. Three new fatalities reported from Karnataka and Gujarat took the death toll due to the viral disease to 5,33,340, as per the ministry’s data updated at 8 am (28th Dec, 2023). At present, India’s COVID-19 case tally stands at 4,50,10,189, whereas the national recovery rate stands at 98.81 percent, according to the ministry’s website. The COVID-19 fatality rate stands at 1.19 percent. Amid growing concerns around the rising cases of COVID-19 sub-variant JN.1, so far a total of 109 cases have been detected in India till Wednesday. The highest contributor of the cases is Goa with a spike of 34 cases reported in a single day on Monday (25th Dec, 2023) [17]. As per the daily data of last 24 h released on Wednesday, a maximum of 36 cases of the new variant were reported from Gujarat, 34 were reported from Karnataka, 14 from Goa, 09 from Maharashtra, 06 from Kerala, and, four from Rajasthan. In addition to this, Tamil Nadu reported four COVID-19 new variant cases and Telangana reported two, reported ANI citing sources. In a sigh of relief, most of the cases reported don’t represent any clustering in areas. Moreover, most of the JN.1 subvariant cases have mild symptoms. Meanwhile, the total number of active cases of COVID-19 in the country stood at 4,054, with the highest number of cases coming from Kerala. “37 COVID-19 cases are from Goa, 344 from Karnataka, 3128 from Kerala, and 50 from Maharashtra”, according to Health Ministry data [18].

Alertness and awareness (AAA)s

As with all viruses, SARS-CoV-2, the virus that causes COVID-19, will continue to evolve as long as it continues to spread. The more that the virus spreads, the more pressure there is for the virus to change. So, the best way to prevent more variants from emerging is to stop the spread of the virus [19].
Follow these measures to protect yourself and others from all SARS-CoV-2 variants:
- Wear a mask when in crowded, enclosed, or poorly ventilated areas, and keep a safe distance from others, as feasible
- Practice respiratory etiquette – covering coughs and sneezes
- Clean your hands regularly with soap and water or alcohol-based sanitizer
- Stay up to date with vaccinations, including additional doses
- Stay home if you are sick
- Get tested if you have symptoms or you’ve been exposed to SARS-CoV-2

Conclusions

JN.1 is one of the most immune-evading variants of COVID-19. Few suggest that S:L455S contributes to increased immune evasion, which partly explains the increased effective reproductive effect of JN.1. Whether JN.1 will trigger a fresh wave of COVID-19 cases similar to those caused by Alpha or Omicron in previous years is still up in the air. Few cases of JN.1 have been reported, which thus this will probably be one of several variations that arise throughout the pandemic that seem concerning but end up being rather small. It appears like JN.1 is starting to slow down and plateau in comparison to earlier this month. But rather than becoming aware of these signs – symptoms and hazards after they spread, it is imperative to prepare ourselves well before. Another wave of cases might probably happen as winter approaches, and JN.1 can a potential route for that to happen.

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