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Research Article

COVID-19 Variants: Molecular Insight into Mutations

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Abstract

The purpose of this study was to summarize the knowledge available on mutations in SARS Cov-2 variants which can help in understanding the mutation pattern and to aid new drug development. Further, we have tried to gather the information available regarding the latent variants i.e. Omicron and IHU variants. So, for this, we have used databases like GISAID and Next strain to get the mutation information. And we have also done a sequence similarity search of emerging variants with the Wuhan reference strains. Also, we have discussed the latest WHO guidelines that need to be followed to tackle this 3rd wave of Covid-19.

Keywords: Mutations; SARS Cov-2 Variants; Doubling Time; Spike Structure

Introduction

The advent of pandemic conditions results in the dissemination of the disease and its concerning complications. The lethality of the virus becomes a matter of public concern and it is inaccessible to predict whether a pandemic will be mild or lethal. The persistence of the outbreak demands high-level, regional, and international coordination to strengthen response efforts to immediately end this pandemic [1]. Accurate and credible circulation of precise information about the situation could help in decreasing the pandemic spread and associated understanding in the population.

COVID-19 is an open-ended public health concern worldwide. In late December 2019, numerous health facilities in the city of Wuhan, China reported a bunch of patients who were diagnosed with pneumonia of undiscovered cause. These cases were associated with a wet animal and seafood wholesale market in Hubei Province, Wuhan, China. Lower respiratory tract samples of these patients were detected with a novel coronavirus [2]. There are various clinical features from mild to acute life-threatening disease which include major complications like dry cough, shortness of breath, muscle pain, the feeling of discomfort, illness, chills, and fever. 2019-nCoV belongs to the coronaviridae family of genus Betacoronavirus and subgenus Sarbecovirus. It possesses (+) ssRNA genome size from 26 to 32 kb in length [3]. Approaching and re-approaching diseases are always a possible challenge to the healthcare system globally.

Clinical features

The clinical features of the lethal virus range from mild to acute life-threatening disease which include major complications like fever, muscle pain, the feeling of discomfort, illness, chills, and dry cough. Shortness of breath may also develop later in the course of the illness. The effect of this virus may also result in multi-organ dysfunction and acute respiratory distress syndrome.

Virus mutants

All viruses, including SARS-CoV-2, that causes COVID-19, mutate over time. Most mutations have little to no impact on the virus' properties. However, some mutations may affect the virus's properties, such as how easily it is transmitted, the associated disease severity, or therapeutic medicines, the performance of vaccines, diagnostic tools, or further public health and community measures [4].

Variants of concern (VOC)

A variant of concern is that strain of SARS-CoV-2 variant that meets the following criteria and changes at a degree of global health significance:

- Exaggerated transmissibility rate and epidemiological changes
- Upsurge in prevalence and disease representation
- Reduced effectiveness of community and government measures according to WHO's 2022 data.

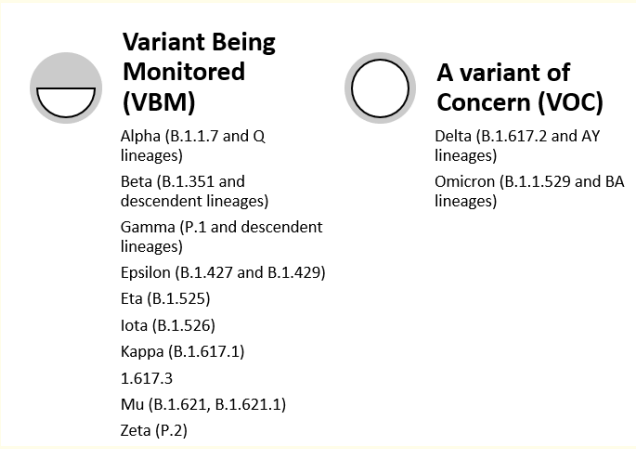

Figure 1: The SIG Variant classification scheme shows two main classes of SARS-CoV-2.

Material and Methods

Data Collecting and Data Processing- The list of mutations (Table 1) reported in new strains of SARS-CoV-2 variants have been prepared using the GISAID database (https://www.gisaid.org/), Nextstrain database (https://nextstrain.org/) and published literature. The Accession number of different strains was used for sequence similarity search using the NCBI tool (https://blast.ncbi.nlm.nih.gov/). Based on the available sequence of SARS-CoV-2 variants the Spike protein structure was modeled using the Swiss model (https://swissmodel.expasy.org/) and the mutation in spike proteins residues were analyzed using Venn diagram.

S. No	SARS-CoV-2 clades	Genbank accession	Mutations
1	19A	OK475246	N: C19220T, T23284C, A23403G, C23604G, G24410A, T26767C
			ORF1b: A1918V
			S: D614G, P681R, D950N
			M: I82T
2	19B	MZ664556	ORF1a: K1781E, H2092Y, R2115S, M3655I
			S: A222V, D253Y, E554A, D614G
			ORF3a: T32I, Q57H
			ORF8: W45C, L95F
			N: Q7K, S202N

3	20A	OK234231	ORF1a: T568I, T2283I, S2293G, I2790T, T3117A, A3143V, R3163S, S3675-, G3676-, F3677
			ORF1b: P314L, G662S, P1000L
			S: L18R, H69-, V70-, T95I, R158S, N440K, E484K, D614G, A688V, N764K
			N: N213Y
			ORF9b: T83I
4	20B	OK232852	ORF1a: E1196V, K2511N, T2936I, A3209V, T3284I, S3675-, G3676-, F3677
			ORF1b: P314L, P976L, A2513S, D2576Y, V2371M
			S: P681H, T95I, Y144-, E484K, D614G, D796H
			M: I82T
			ORF8: E106
			N: R203K, G204R, A208-, R209G, M234I
5	20C	MZ511679	ORF1a: T265I, H1545Y, A1679S, K3162E, L3201P, A3209V, S3675-, G3676-, F3677-, V3847I
			ORF1b: P314L, S1779I
			S: D80G, Y144-, F157S, L452R, D614G, P681H, T859N, D950H, P1079S
			ORF3a: A39T, P42L, Q57H, P104F
			ORF8: T11I, A51S
			N: T205I, R209I, M234I
			ORF9b: P17L
6	20D	OK001901	ORF1a: E102K, A859V, T1246I, S3687L, D1639N, P2287S, P2852S, D2980N, L3691S
			ORF1b: D1028Y, P314L
			S: R346S, L452R, D614G, A899S, W152R
			M: I82T
			N: G212V, R203K, G204R
7	20E (EU1)	MZ054387	ORF1a: T1538N
			ORF1b: P314L, A1884S
			S: A222V, A262S, P272L, D614G
			ORF3a: G172C, V256
			N: G96V, A220V, T271I
			ORF9b: V93L
8	20F	MW277409	ORF1a: I300F, A2355S
			ORF1b: P314L, N902S
			S: S477N, D614G, V1133F
			ORF8: I39T
			N: R203K, G204R

9	20G	MZ462166	ORF1a: T265I, V1063I, S2246L, N2361K, M2606I, L3352F
			ORF1b: P314L, T1555I, N1653D, R2613C
			S: S477N, D614G, Q677H
			ORF3a: Q57H, G172V
			ORF8: S24L
			N: P67S, P199L, Q418H
10	20H (Beta, V2)	OL779036	ORF1a: S3675-, T265I, G3676- K1655N, K3353R, F3677-, T4311I
			ORF1b: P314L
			S: D215G, A243-, K417N, E484K, D614G, A701V, D80A, L241-, N501Y
			ORF3a: V112F, S171L, Q185H, Q57H
			E: P71L
			N: T205I
11	20I (Alpha, V1)	OM141401	ORF1a: T1001I, A1708D, I2230T, K3353R, S3675-, G3676-, F3677-, L3915F
			ORF1b: P314L, P976L, D1028N
			S: H69-, V70-, D138Y, Y144-, D215G, L241-, L242-, A243-, Q493R, G496S, Q498R, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H
			M: L16I
			ORF8: Q27*, R52I, K68*, Y73C
			N: D3L, R203K, G204R, S235F
12	20J (Gamma, V3)	OK252994	ORF1a: E57K, S1188L, K1795Q, P3371S, S3675-, G3676-, F3677
			ORF1b: E1264D, P314L
			S: T20N, P26S, D138Y, R190S, R246G, K417T, D614G, H655Y, N679K, T1027I, V1176F, L18F, E484K, N501Y
			ORF3a: S74F, L106F, T151I, S253P
			ORF8: E92K
			N: R203K, G204R, P80R
			ORF9b: Q77E
13	21A (Delta)	OL779078	ORF1a: P309L, P1640L, H2092Y, A3209V, V3718A
			ORF1b: G662S, P1000L, H2285Y, P314L
			S: G142D, E156-, F157-, R158G, Q414K, T478K, D614G, P681R, D950N, T19R, L452R
			ORF3a: I47V, M125I, S26L
			M: I82T
			ORF7a: A105E, L116F, T120I, V82A
			ORF8: D119-, F120
			N: D63G, L139F, D377Y, R203M, G238C, R385K
			ORF9b: T60A

14	21B (Kappa)	MZ343477	ORF1a: V54I, T3646A, T1000I, T1567I,
			ORF1b: V666I, M1352I, K2310R, P314L, S2312A
			S: G142D, D614G, E484Q, E154K, V382L, L452R, P681R, Q1071H, D1153Y
			ORF3a: S26L
			ORF6: I33T
			ORF7a: V82A, K119N
			N: D377Y, R203M
15	21C (Epsilon)	MW990641	ORF1a: T265I, Y621C, L3930F, I4205V
			ORF1b: T634I, P314L, D1183Y
			S: S13I, L452R, W152C, D614G
			ORF3a: E226A, Q57H,
			ORF8: V100L
			N: M234I, T205I
16	21D (Eta)	OL601960	ORF1a: K247N, T2007I, S3675-, G3676-, F3677
			ORF1b: P314F
			S: Q52R, A67V, H69-, V70-, Y144-, K150N, E484K, F888L, D614G, Q677H
			ORF3a: S92L
			E: L21F
			M: I82T
			ORF6: F2M
			N: A12G S2M, T205I, D3Y
			ORF9b: H9D
17	21F (Iota)	MZ390544	ORF1a: T265I, D935G, S2981F, L3201P, S3675-, G3676-, F3677
			ORF1b: Q1011H, P314L
			S: L5F, D253G, D614G, A701V, V1230M, T95I, E484K
			ORF3a: Q57H, A33S, P42L
			ORF8: V116F, T11I
			N: P199L, M234I
18	21G (Lambda)	OL622101	ORF1a: Q990L, T1246I, F2387V, L3027F, P2287S, L3201P, G3278S, S3675-, G3676, T3255I,
			ORF1b: P314L
			S: L249-, G75V, R246-, S247-, Y248-, , T250-, P251-, D253N, L452Q, F490S, D614G, T859N, T76I, G252-
			N: R203K, G204R, T366I, P13L, G214C
			ORF9b: P10S

19	21H (Mu)	OK302879	ORF1a: T1055A, E1237K, T1250I, T1538I, Q3729R, T3090I, T3255I, T4083M
			ORF1b: P314L, P1342S, H1213Y
			S: T95I, Y145N, R346K, D614G, D950N, Y144S, P681H
			ORF3a: V256, Q57H
			ORF7b: E39*
			ORF8: T11K, F120L, P38S
			N: T205I
			ORF9b: T72I
20	21I (Delta)	OL779011	ORF1a: P1640L, A3209V, V3718A, T3750I
			ORF1b: P314L, G662S, P1000I, H2010Y
			S: T19R, E156-, R158G, A222V, L452R, D614G, P681R, D950N, G142D, F157-, T478K
			ORF3a: S26L
			M: I82T
			ORF7a: N52-, T120I, K53-, V82A
			ORF8: F120, D119-
			N: D63G, D144Y, R203M, D377Y
			ORF9b: T60A
21	21J (Delta)	OL640778	ORF1a: V2930L, A1306S, P2046L, T3255I, P2287S, T3646A
			ORF1b: G662S, F183V, P314L, , A1918V, P1000L
			S: T19R, E156-, F157-, R158G, D614G, P681R, D950N, G142D, T478K, L452R
			ORF3a: S26L
			M: I82T
			ORF7a: T120I, V82A,
			ORF7b: T40I
			ORF8: D119-, F120
			N: R203M, G215C, D63G, D377Y
			ORF9b: T60A
22	21K (Omicron)	OL672836	ORF1a: A2710T, K856R, S2083-, L2084I, L3674-, S3675-, G3676-, I3758V, T3255I, P3395H
			ORF1b: I1566V, P314L
			S: K417N, S477N, A67V, H69-, V70-, T95I, G142-, V143-, Y144-, Y145D, N211-, Q493R, L212I, G339D, T547K, S371L, S373P, Q954H, S375F, D796Y, N440K, G446S, T478K, E484A , G496S, Q498R, N501Y, Y505H, D614G, H655Y, N679K, P681H, N764K, N856K, N969K, L981F
			E: T9I
			M: Q19E, D3G, A63T
			N: G204R, P13L, E31-, S33-, R203K, R32-
			ORF9b: E27-, N28-, P10S, A29

23	21M (Omicron)	OM141265	ORF1a: K856R, L3674-, A2710T, I3758V, S2083-, L2084I, T3255I, P3395H, S3675-, G3676-
			ORF1b: Q866R, I1566V, P314L
			S: A67V, V70-, T95I, G142-, Q493R, Y144-, Y145D, N211-, N764K, N969K, L212I, G339D, R346K, S371L, G496S, Q498R, H69-, N501Y, Y505H, T547K, D614G, H655Y, D796Y, N856K, Q954H, L981F, V143-
			E: T9I
			M: A63T, Q19E, D3G,
			N: R32-, S33-, R203K, E31-, P13L, G204R
			ORF9b: P10S, E27-, N28-, A29
24	IHU	Not Available	S: D215H S: R346S S: N394S S: Y449N - S: E484K S: F490S S: N501Y S: D614G S: P681H S: T859N S: D1139H
			M: I82S
			N: T205I, D22Y N
			ORF1a: P309L ORF1a, T3750I, D3222N
			ORF1b: P314L, V1294A- P1570S, V1961F
			ORF3a: T32I, Q57H
			ORF8: C37R, Q27,
			ORF9b: Q18H, P10L

Table 1: List of mutation reported in emerging SARS-CoV-2 variant.

Result and Discussion

Based on similarity search analysis between the Wuhan reference strain (NC_045512) and the different covid-19 variants, we can say the 19A variant shows very little similarity (95.24%) while delta and omicron show 99.92% and 99.82% similarity respectively (as shown in Figure 2). The mutation can help the virus in increasing the infectivity, if we analyze the data of mutation in spike protein, we can see most of the mutations are in the receptor-binding domain (as shown in Figures 3 and 4).

Figure 2: Sequence Alignment of all the SARS-CoV-2 variants.

Figure 3: Mutation in Spike protein (shown as grey surface) of SARS Cov-2 variants: A- Wuhan reference strain, B- Omicron, C- Beta, D- Epsilon, E- Delta, F- Gamma.

Figure 4: Venn diagram showing common and unique spike mutation in SARS Cov-2 variants.

The Omicron variant

WHO's reports show, the first recorded confirmed infection by Omicron could be traced back to a specimen collected on November 9, 2021, and the prime Omicron sequence available was from a specimen collected on November 11, 2021, in Botswana. Ever since the identification of Omicron, it appears to spread rapidly.

The Omicron variant is categorized as VOC by WHO, which recorded the shortest interval period of reclassifying a variant from VUM to VOC and subsequently brought about great public distress. The analysis of sequences of SARS-CoV-2 variants confirms that Omicron is substantially distinct from the rest of the SARS-CoV-2 variants such that it is challenging to identify its closest relative. The results of phylogenetic studies illustrate that the Omicron variant likely has deviated early from other SARS-CoV-2 variants rather than being developed from one of the previous VOCs [5].

It is hypothesized that for a certain period the Omicron variant might have evolved in immunocompromised hosts (e.g., HIV patients co-infected by SARS-CoV-2), or in a nonhuman species and recently start infecting human beings again.

Characteristics of Omicron variant

Since January 2020, three big waves of COVID-19 outbreaks have been recorded in South Africa and many other countries, two of them being caused by the Beta and Delta variants respectively. The epidemiological data showed that the percentage of infections associated with the Beta variant increased to ~50% of the total daily infections within approximately 100 days since its outbreak. The infection percentage of the Delta variant, however, rose to ~80% during the same period, echoing higher transmissibility among people for Delta than for the Beta variant. In contrast, the percentage of Omicron infection reached ~90% within approximately 25 days in South Africa [6].

The early doubling time of the Beta, Delta, and Omicron variants was calculated to be about 1.7, 1.5, and 1.2 days, respectively (as shown in figure 5). These data indicate that the Omicron variant is probably more infectious than the Delta and Beta variants.

It is also noteworthy that a recent retrospective study based on the population-wide epidemiological data in South Africa indicates an increased risk of SARS-CoV-2 reinfection associated with

Figure 5: Pictorial representation of SARS Cov-2 variants doubling time.

Omicron. The possibility of a new wave of COVID-19 epidemic in South Africa and even around the world therefore should not be ignored [7].

With the outbreak of Omicron, it can be said that it may be the last wave considering the graphics of infections in India and around the world. There is a possibility that we will have developed a form of immunity, either through vaccination or through getting infected or both. To date, there is limited data availability on vaccination effectiveness for Omicron. Primary outcomes of vaccination effectiveness have been released by South Africa and the UK but this should be considered or correlated carefully because of the small comparative data and study biased [8]. Consequences from the UK, shows a great decline in effect of vaccination showing symptoms for Omicron in comparison to Delta after 2 doses of either AstraZeneca-Vaxzervria or Pfizer BioNTech-Comirnaty vaccine. However, a Pfizer BioNTech-Comirnaty booster showed high effectiveness, that was slightly less or proportionate to that against Delta [9].

The IHU variant (B.1.640.2)

B.1.640.2 is so new that it doesn't have an official name yet, but it's being called the IHU variant because investigators with IHU Mediterranean Infection discovered it. Their study, also on medRxiv, states that the B.1.640.2 variant contains "46 mutations and 37 deletions resulting in 30 amino acid substitutions and 12 deletions [10] as shown in table 1.

The XE variant (Omicron BA.1)

Recently a new variant of covid-19 has been found in the United Kingdom and it has been predicted that this recombinant variant has more than 10% transmission rate than BA.2.

Conclusion and Perspective

With the increase of viral pandemic day by day, specific measures must be taken to restrict the viral spread globally. The numbers of infected patients are manifold and the medical healthcare facilities are finite. To defeat this, government health care systems should be designed in a way to safeguard the infected people and also the people who are on the verge of getting infected, as the safety of medical staff and the uninfected population is a major concern [11]. Awareness drives and programs must be initiated again to inform the people and the health care staff about the return of the pandemic and also how one can protect them from getting infected. To reduce the damage linked with the pandemic, new strategies of public health and infection control methods and measures are necessary to limit this outbreak. Governments have implemented many public health and infection control measures which help in reducing the risk globally. Social distancing is highly essential to restrict human-to-human transmission [12]. The Delta variant is still dominant worldwide, and enhanced efforts to control Delta will benefit the control of Omicron, regardless of how the situation with Omicron worldwide unfolds. Countries should optimize their response for Delta which will benefit responses to any future variants as well as Omicron.

WHO recommends the following priority actions

Ensure prime warning systems are in place, composed of multiple indicators like growth rate, effective reproduction number, case frequency, and test positivity proportion. It is also crucial to record indicators related to disease acuteness and pressure on health care systems (e.g., bed occupancy of the general ward and intensive care units and health care worker exposure and burnout).

Where scope exists and in coordination with the global community, execute studies for improving the knowledge on the spreading rate, strength of vaccination, acuteness, the persuasiveness of community measures and safety (CMS) against this new mutant (Omicron), diagnosis, immunity, population risk approach, knowledge, attitude and behavior towards CMS, vaccines, and tests or other relevant characteristics.

Specimen collection strategies for detection of Omicron (random or selected) should be reported interconnecting the relative prevalence reports of Omicron to allow an insight into the representativeness of the prevalence of Omicron.

That's specifically admissible to infection preventionists (IPs) and other health care professionals who find themselves yet again on the frontlines of another deluge.

According to the Centers for Disease Control and Prevention (CDC), long COVID "is a range of symptoms that can last weeks or months after primarily being infected with the virus that causes COVID-19 or can appear weeks after infection. Long COVID can happen to anyone who has had COVID-19, even if their illness was mild, or if they had no symptoms".

Conflicts of Interest

The authors have no conflict of interest.

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