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Review Article

The genomic characteristics of SARS-CoV-2 and emergence of SARS-CoV-2 variants

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ABSTRACT

The 2019 coronavirus disease (COVID-19) causes global pandemic public health problem in the world. COVID-19 has been defined as a disease that can be transmitted from human to human via respiratory droplets. Considering COVID-19 pandemic, the publication of articles on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease induced by this virus are dramatically increased. This review article aims to gather the knowledge associated to the genomic characteristics and evolution of SARS-CoV-2 strains, thus enlightened us in understanding SARS-CoV-2 pathogenecity that will helps in developing new mitigation strategies. The full genome characterization of SARS-CoV-2 give insight into the virus evolution and adaptation in different populations across the globe. As different variants of SARS-CoV-2 strains circulating in various regions and populations, further investigations are necessary to warrant the impact of treatment on different strains.

1. Introduction

A novel coronavirus, known as 2019-nCoV by the World Health Organization (WHO) detected in the earlier phase of the disease outbreak has been determined as the third coronavirus that can infect human populations after the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome coronavirus (MERS-CoV)[1] (Chen, 2020; Perlman, 2020; Wang et al., 2020). The 2019-nCoV can induce a severe respiratory illness like two previous CoVs, SARS-CoV of 2002 and MERS-CoV of 2012 (Cui et al., 2019; de Wit et al., 2016). 2019-nCoV strain is more pathogenic than SARS-CoV and less virulent

[1] WHO (2020) Statement on the Meeting of the International Health Regulations. Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV); 2005. [online]. Website https://www. who. int/news-room/detail /30-01-2020-statement-onthe-second-meeting-of-the-international-health-regulations 2005 [accessed date 25.08.2020]

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than MERS-CoV and was reported to have high person-to-person transmission ability (Chen, 2020).

Coronaviruses, the members of the family Coronaviridae in the order Nidovirales, are the small enveloped RNA virus with genome of positive polarity and measures approximately 30 kbp (Schoeman and Fielding, 2019; Woo et al., 2010). CoVs have been classified into 4 groups (alpha; α- CoV, beta; β-CoV, gamma; γ-CoV and delta; δ-CoV coronaviruses) according to genetic and antigenic criteria, and SARS-CoV-2 belongs to β-CoV genus (Perlman and Netland, 2009; Schoeman and Fielding, 2019; Vlasova et al., 2007).

In this review, we aim to analyse the genomic characterization of SARS-CoV-2 strains and evolution of SARS-CoV-2 strains.

2. Genome characteristics of SARS-CoV-2 strains

As on January 2021, there are more than 327,000 complete and partial genomes of SARS-CoV-2 have been submitted in to the GISAID database[2]. Whole genome sequencing and phylogenetic analysis are used to determine the genetic drift in the virus genome. These tools also help in understanding the evolution of SARS-CoV-2 within humans, in tracing infection pathways and to design preventive strategies. Genome data can give insights into the growing epidemic which is not always obvious from the epidemiological data alone (Volz et al., 2020). As the virus transmitted rapidly throughout a population, it will accumulate mutations in its genetic code (Volz et al., 2020). Hence by identifying variations in genetic sequences from the samples collected from different patients across the globe, it is possible to reconstruct the evolutionary history of the ongoing pandemic (Volz et al., 2020).

The findings of researchers on SARS-CoV-2 genome characterization is summarized (Table 1). In early 2020, the first report on the virus sequencing indicated that SARS-CoV-2 is closely related to bat-extracted SARS-like coronavirus with more than 96% identity with bat CoV, RaTG13 (Zhou et al., 2020a; Zhou et al., 2020b). The far distant of the SARS-CoV-2 genome to other Corona viruses (CoVs) include the SARS-CoV and MERS-CoV. Bat has been proposed to be the original host of SARS-CoV-2 and infected animal sold at seafood market in Wuhan, China exemplify an intermediate host. The phylogenetic tree showed that there was a shorter distance between SARS-CoV-2 and RaTG13 CoV compared to pangolin CoV. Spike (S) protein of SARS-CoV-2 is closest to bat RaTG13 followed by the pangolin CoV (Lopes et al., 2020). Pangolins might play a role in the SARS-CoV-2 transmission from animal to human due to closer position of SARS like-CoV-2 obtained from pangolins (Lopes et al., 2020). Infection by SARS-CoV-2 has been reported in different domestic animals during natural or experimental conditions but their direct involvement in COVID-19 pandemic is not known and the intermediate host is unclear yet (Tazerji et al., 2020).

A study also shown that angiotension-converting enzyme 2 (ACE-2) is the receptor for SARS-CoV-2 in humans which is also a receptor for SARS-CoV (Lu et al., 2020). Phylogenetic super tree approach revealed two mutation sites in the SARS-CoV-2 S protein. Mutation located between the receptor-binding domain (nucleotide position at 451-509) confer aspartic acid to glycine at amino acid position 614 (D614G), whereas mutation at the polybasic cleavage site (nucleotide position at 682-685) led to amino acid changes from histidine to tyrosine at position 49 (H49Y) (Li et al., 2020). The binding capability of the virus with human host ACE2 receptor possibly has been regulated by these mutations which leads to variable ability of the virus to infect different host (Li et al., 2020).

Single nucleotide polymorphisms (SNPs) analysis from the SARS-CoV-2 infected patients who travelled across the continents able to explain the possible variation and relations between the strains (Table 1) (Castillo et al., 2020). A couple who had travelling history to Southeast Asia were infected with the virus harboring the same SNPs and the strain's variants were related to strains from Wuhan, China and Taiwan. The patients who travelled to Europe contracted with strains related to Spanish and European isolates (Castillo et al., 2020). Two different variants of strains (S and G variants) were identified in Chile. Phylogenetic

[2] .GISAID database. [online] Website https://www.gisaid.org/ [accessed date 20.01.2021].

analysis shows that the S variant is related to strains in Wuhan, China and Taiwan, while the G variant is related to Spanish isolates (Castillo et al., 2020). These results show that the coincident of contracting infection with strain's variant and the patient's travel record, thus infers about the viral entries to the population.

A group of researchers performed an analysis of the phylogenetic network on 160 complete genomes of SARS-CoV-2 to explain the existence of different variants based on their amino acid changes and grouped them into 3 main clusters: A, B and C (Forster et al., 2020). Nearly half of cluster A were appeared outside East Asia, mainly in the US and Australia. Cluster B is considered as an ancestral type and adapted well in the environment of East Asian population and may have undergone mutation to adapt in the host outside East Asian population. Cluster C is a major European type and absent in the Chinese population (Forster et al., 2020).

A viral quasispecies is a major concern in SARS-CoV-2 pandemic. The SARS-CoV-2 genome is prone to mutation due to constant exposure to selective pressure in new host. The quasispecies occurred as a result of high mutation rates emerge continuously and change in relative frequency. SARS-CoV-2 pandemic has caused a mixture of various strains that lead to generation of quasispecies in human populations (Capobianchi et al., 2020; Tang et al., 2020). The viral genotypes are well defined by different SNPs (Table 1). The presence of mutations in receptor-binding domain of SARS-CoV-2 S protein may result in diversity of the virus and could affect its capability to infect different host (Anderson et al., 2020). The viral quasispecies may provide the background of virus evolution and its adaptation to new hosts.

A group of researchers from Italy, sequenced the locally isolated virus and explained the genomic heterogeneity in SARS-CoV-2 through analysis of SNPs. Three isolates sampled from patients in the same area on the same day, were having identical sequences but having different SNPs, which could be mainly due to synonymous substitutions among the strains. This suggests the occurrences of genetic drift in the virus genome in the area with the highest number of cases where the virus population has a high degree of genomic heterogeneity (Zehender et al., 2020). A recent study has reported antigenic shift in SARS-CoV-2 spike protein from D614G to G614 variant and the variant become the most common form in global pandemic (Korber et al., 2020). Infection with G614 variant showed high viral loads in infected individual, but not associated with increased disease severity.

3. Evolution and emergence of SARS-CoV-2 variants

Mutations that evolved in SARS-CoV-2 lead to the emergence of variants of concern and variants of clinical interest. There are also mutations in SARS-CoV-2 that may help in its transmission which occur alone or together with other variants (Alsobaie, 2021; Banoun, 2021; Lauring and Hodcroft, 2021; Srivastava et al., 2021; Wang et al., 2021a). The effects of each mutation on the protein sequences of SARS-CoV-2 have been summarised (Table 2). Briefly, the D614G mutant is highly transmissible but does not result in severe disease or help the virus in escaping the vaccine induced immunity. The N501Y and K417K mutations changed the shape of viral spike protein, making it bind tighter to human ACE2 positive cells. E484K mutation likely helps the virus in vaccine induced antibody evasion. Both L452R and Q677 mutations made the virus less infectious. Current Omicron variant has N501Y, D614G, K417N, and T478K mutations and so far found to cause mild disease.

4. Variants of concern (VOC)

These are SARS-CoV-2 variants that are more infectious and pathogenic than other circulating viruses (Table 3), and their lineage and mutations occur in the spike protein.

a) Alpha: B.1.1.7 lineage

This lineage of SARS-CoV-2 is 30-50% more infectious than other variants and likely to be lethal. It was first emerged in Britain in December 2020 and spread quickly to other countries at exponential rate (Wang et al., 2021b). It has been idenitifed in over 110 countries. It was first appeared in the USA in January 2021 and now dominate in all 50 states. Although it is more infectious, studies suggest that vaccine still works against it (Wang et al., 2021b). Mutations in this lineage occurs in the spike protein comprise:

- N501Y mutation helps the virus to attach more firmly to human cells. However, this mutation does not help the virus avoid available vaccines;
- P681H mutation helps the virus create new spike protein;
- H69–V70 and Y144/145 deletions change the spike shape and may help in antibodies evasion[3] (Wang et al., 2021b).
- Other mutations include A570D and S106/G107/F108 deletion (Wang et al., 2021b).

b) Beta: B.1.351 lineage

This lineage was first reported in South Africa in December 2020 and spread into neighbouring countries (Happi et al., 2021). It was detected in the USA in January 2020 and since then it has spread to at least 68 countries (Happi et al., 2021). Some vaccines showed reduced protection against spread to at least 68 countries. Some vaccines showed reduced protection against this variant. People who obtain from other variants may be reinfected with B.1.351 variant (Happi et al., 2021). Mutations in this variant occur near tip of the spike protein comprise:

- N501Y mutation helps the virus to attach more firmly to human cells. The B.1.1.7 and P.1 lineages also have this mutation.
- K417N mutation helps the virus bind more firmly to human cells.
- E484K mutation helps the virus with antibodies evasion (Happi et al., 2021).
- Other mutations include L242/A243/L244 and S106/G107/F108 deletions (Happi et al., 2021).

c) Gamma: P.1 lineage

This variant emerged in Manaus, the biggest city in Brazil's Amazon region in late 2020 and was first identified in Japan in four people who contracted P.1 variant on a trip to Brazil (Anand et al., 2021). It became a predominant variant in Brazil and in several other South American cities. It reached the US in January 2021 and now spread to at least 37 countries (Anand et al., 2021).

The P.1 lineage is a close correlative of the B.1.351 lineage and has some of the similar mutations on the spike protein. Infection with the P.1 variant may accomplish the immunity occured after infection by other variants. Mutations in this variant occurs in the spike protein like those in the B.1.351 lineage, but they emerged independently (Faria et al., 2021). The mutations include:

- N501Y mutation helps the virus attach more firmly to human cells. This mutation also detected in the B.1.1.7 and B.1.351 lineages (Faria et al., 2021).
- K417T mutation is at the same location as the K417N mutation in the B.1.351lineage. It may help the virus bind stricter to cells (Faria et al., 2021).
- E484K mutation helps the virus evade from antibodies (Faria et al., 2021; Frampton et al., 2021).
- Other mutations include S106/G107/F108 deletion (Faria et al., 2021).

d) Delta, Kappa: B.1.617 lineage

This variant was first documented in October 2020, is now the widest variant in India and has spread to Britain, US and Israel. This lineage harbours more mutations than other variants as mentioned above (Hoffmann et al., 2021; Khan, 2021). The E484Q and L452R are two prominent mutations in this lineage. E484Q lies at the same location as E484K that might help the virus in antibodies evasion (Hoffmann et al., 2021; Khan, 2021). L452R mutation detected in the B.1.429 variant has been common in strains circulating in California. Evolution of the B.1.617 lineage splits into new lineages including 1.617.1 designated as Kappa and B.1.617.2 designated as Delta (Hoffmann et al., 2021; Khan, 2021).

Variants of Interest (VOI)

SARS-CoV-2 VOI are having mutations that may help in antibodies evasion or bind more strictly to human cells (Table 4). However, they have been determined to be less infectious. The Epsilon variant was detected in California in January 2021. By early February, more than half of samples detected in Los Angeles has been identified to be infected with this variant and subsequently declined in most parts of the US (Ulloa et al., 2021). This variant belongs to associated lineages in California known as B.1.427 and B.1.429 (Ulloa et al., 2021). Studies suggest it may be more contagious than earlier variants of the virus; however it has been

[3] . Coronavirus Variants: Latest News and Updates - The New York Times [online] Website https://www.nytimes.com/interactive/2021/health/coronavirus-variant-tracker.html [accessed 27 July 2021].

Table 1. Phylogenetic analysis of SARS-CoV-2 strains

References	Sample, country of origin	Method and Analysis	Results
Lu et al., 2020	Ten genomes of 2019-nCoV from 9 patients in Wuhan, China	Sanger sequencing (full-genome) Analysis: • Phylogenetic Homology modelling	10 genomes = 99.98% sequence identity 88% identity with two bat-obtained SARS-like coronavirus (bat-SL-CoVZC45 and bat-SL-CoVZXC21) Distant similarity: ~ 79% from SARS-CoV and ~50% from MERS-CoV Genus: Betacoronavirus Subgenus: Sarbevirus Had binding receptor similar to receptor-binding domain structure of SARS-CoV
Castillo et al., 2020	Four cases, travelled to Europe and Southeast Asian	Next generation sequencing Phylogenetic analysis	Presence of SNPs that generate amino acid changes • 1st and 2nd cases (couple) Nonsynonymous mutations inexonuclease (V290F) and N-nucleocapsid phosphoprotein (D103Y) • 3rd case Mutations in transmembrane domain 2 TM2 (F308Y) and N-nucleocapsid phosphoprotein (S197L) • 4th case Mutations inpapain-like proteinase (A225V), RNA-dependent RNA polymerase (P323L), S-surface spike glycoprotein (D614G) and N-nucleocapsid phosphoprotein twice (R203K, G204R) A maximum likelihood phylogeny tree showed that the1st and 2nd sample were similar to strains from Wuhan, China and Taiwan. The 3rd sample was clustered together with Spanish isolates. The 4th sample was grouped with isolates from Switzerland, Netherlands and Germany
Foster et al., 2020	160 complete SARS-CoV-2 genomes	Phylogenetic network	3 variants were classified based on different amino acid changes: type A, type B and type C Two subclusters of A were identified due to the synonymous mutation T29095C -T-allele subcluster were identified in 4 Chinese, 3 Japanese and 2 Americans -C-allele subcluster were identified in 5 individuals from Wuhan and 8 other East Asians and neighboring countries -Nearly half (15/33) are found in the US and Australia
			Cluster B was reproduced from A by two mutations i.e., T8782C (synonymous) and C28144T (nonsynonymous)
			Cluster C was differed from its parent type B by the G26144T mutation (nonsynonymous) which confer a glycine to a valine • Detected in Europe, Hong Kong, Singapore, South Korea and Taiwan. • Unavailable in the mainland Chinese sample.
Tang et al., 2020	103 SARS-CoV-2 genomes	Population genetic analysis	The similarity of SARS-CoV-2 as shown below (similarity decreases): • RaTG13 (bat SARS-related) • Guangdon Pangolin SARS-CoV • Guangxi Pangolin SARS-CoV • ZC45 and ZXC21 (bat SARS-related) • human SARS-CoV • BM48031 (bat SARS-related) Genetic analysis of 103 SARS-CoV-2 indicates that SARS-CoV-2 evolved into two major types i.e., L and S type. The type L is more prevalent (~70% strains) than type S (~30% strains)
Capobianchi et al., 2020	Two Chinese spouses 87 full genome SARS-CoV-2 sequences	Viral culture RT-PCR Next Generation Sequencing	Virus isolation: • successful obtained from sputum of Patient 1 • unsuccessful from NP swab of Patient 2 Two nonsynonymous changes from Patient 1 sample: • G11083T • G26145T One additional synonymous substitution in Orf1a (A2269T) Phylogenetic analysis: • The G26145T substitution in Italian isolate was also identified in isolates from France, Taiwan, US and Australia
Zehender et al., 2020	Three SARS-CoV-2 genomes in Lombardy, Italy	Illumina Deep Sequencing Alignment with 157 SARS‐CoV‐2 genomes	The three Italian genomes clustered in clade A. Others in clade A includes two genomes from outbreak in Lombardy, 3 isolates from Europe and two from Latin Americans. D614G mutation in the S gene was identified in clade A.

Table 2. Mutations of concern detected in SARS-CoV-2 genome

References	Mutation	Lineage	Description
European Centre for Disease Prevention and Control[4]	D614G (DOUG)	B.1	Early in the pandemic, the mutation was emerged in eastern China and then spread around the world displacing the naive SARS-CoV-2 strains. This variant is highly transmissible, though it does not results in severe disease or help the virus in escaping the vaccine induced immunity.
European Centre for Disease Prevention and Control[4]	N501Y (NELLY)	Several	This mutation emerged independently in several variants, containing B.1.1.7, B.1.351 and P.1. This mutation results in changes of the viral spike protein shape due to its location near the tip of the SARS-CoV-2 spike. The changing of viral spike shape makes it to bind tighter with human ACE2 positive cells.
Coronavirus Variants: Latest News and Updates[3] cited 22 June 2021	E484K or "EeK"*	Several	This mutation has been appeared in Argentina, Brazil, Britain, Canada, Japan and US. It was detected independently in several lineages containing B.1.351 and P.1. This mutation also emerges near top of the SARS-CoV-2 spike. This change likely helps the virus in vaccine induced antibody evasion.
Coronavirus Variants: Latest News and Updates[3] cited 22 June 2021	K417K	Several	Detects in several lineages comprising B.1.351 and P.1. This mutation helps the virus bind more tighter to ACE2 positive cells.
Coronavirus Variants: Latest News and Updates[3] cited 22 June 2021	L452R	Several	Predominantly detected in California, however indicated to be less infectious.
Coronavirus Variants: Latest News and Updates[3] cited 22 June 2021	Q677	Several	Identified in seven US lineages, however indicated to be less infectious.
Coronavirus Variants: Latest News and Updates[3] cited 26 Nov 2021	N501Y D614G K417N T478K	Several	Identified in several lineages, however indicated to be less infectious.

*Nicknamed "Eek" is given by some scientists.

Table 3. SARS-CoV-2 variants of concern, their lineage and mutations.

References	Name	Lineage	Other names	Key mutations in the spike protein
Coronavirus Variants: Latest News and Updates[3] ; Wang et al., 2021b	Alpha	B.1.1.7	- VOC 202012/01 - 20I/501Y.V1	- N501Y - P681H - H69-V70 and Y144/145 deletions
Happi et al., 2021	Beta	B.1.351	20H/501Y.V2	- N501Y - K417N - E484K
Faria et al., 2021; Frampton et al., 2021	Gamma	P.1	20J/501Y.V3	- N501Y - K417T - E484K
Hoffmann et al., 2021; Khan, 2021	Kappa	B.1.617.1	Double mutant	- E484Q - L452R
Hoffmann et al., 2021; Khan, 2021	Delta	B.1.617.2	Double mutant	- E484Q - L452R

[4] . SARS-CoV-2 variants of concern as of 24 May 2021. [online] Website https://www.ecdc.europa.eu/en/covid-19/variants-concern [accessed 25 June 2021].

Table 4. SARS-CoV-2 variants of concern and their characteristics.

References	Name	Lineage	Mutations	Status
Ulloa et al., 2021	Epsilon	B.1.427/429	CAL.20C	L452R
Ulloa et al., 2021	Zeta	P.2	Information not available	First identified in Brazil
Ulloa et al., 2021	Eta	B.1.525	Some of the same mutations as B.1.1.7	Spreading in New York
Ulloa et al., 2021	Theta	P.3	Information not available	First identified in Philippines
Ulloa et al., 2021	Iota	B.1.526	Strains may harbour E484K or S477N mutation	Spreading in New York

outcompeted by B.1.1.7 variant. The Eta variant was first appeared in December 2020 and spread to New York (Ulloa et al., 2021). It carries same mutations as the B.1.1.7 lineage containing E484K, Q677H, and H69-V70 deletion. The Iota variant first reported in November 2020 and by mid-February in about 27% of New York city viruses (Ulloa et al., 2021). This variant appears in two forms: E484K helps to evade from antibodies and S477N helps to bind more tightly to human cells[5]. The knowledge of virus evolution and the epidemiology of SARS-CoV-2 variants[3] make us to better understand the virus behaviour which have a great impact on society and global economy.

Adaptation of SARS-CoV-2 virus during infection in human populations make the virus easily to mutate in order to survive in the host. Various mutations and combinations of mutations alter the behaviour of the virus. Recently, a new variant of SARS-CoV-2 has been detected which has a large number of mutations compared to other VOCs and considered arise from B.1.1.529 lineage. This variant has been designated as variant of concern by WHO [6]on 26 November 2021 and named as Omicron. Researchers recognized Omicron to its distinctive combinations of more than 50 mutations including mutations in earlier reported variants such as Alpha and Beta. These mutations could increase the speed of coronoaviruses spreading and also might help coronaviruses evade antibodies produced by vaccines. Omicron variant was first reported in Bostswana and South Africa in November 2021 (Doria-Rose et al., 2021).

Since then, the variant has been spread in more than 90 countries. It is still unclear whether Omicron is more transmissible than other variants, comprising Delta (Asamoah et al., 2021). Large epidemiological studies are required to understand the transmission factors of Omicron among humans. Data on the impact of Omicron on the severity of disease and symptoms associated with Omicron infection are still lacking.

Investigations on this SARS-CoV-2 variant are underway all over the world to understand its behaviour and the impact of the infection in particular for the most vulnerable people, thus helps us in developing the prevention strategies.

Conclusion

In conclusion, the full genome characterization of SARS-CoV-2 has provided insights into the virus evolution and adaptation in different population across the globe. As different variants of strains circulating in various regions and population, the impact of treatment on different strains warrant further investigation. The diagnostic tests developed to detect the viral

[5] . EPIDATUM. COVID-19 NEW DEATHS PER DAY. [online] Website https://epidatum.com [accessed date 10.01.2022].

[6] . Classification of Omicron (B.1.1.529): SARS-CoV-2 Variant of Concern [online] Website https://www.who.int/news/item/26-11-2021-classification-of-omicron-(b.1.1.529)-sars-cov-2-variant-of-concern [accessed date 27.12.2021].

antigen from the beginning of pandemic might need better optimization and improvements to detect new viral variants or strains which might arise from future COVID pandemics.

Conflict of interest

The authors declare that they have no conflict of interest.

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