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Review article

Evolutionary Dynamics of the Emergent SARS-Cov-2 Variants: Just Within a Year of Circulation

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ABSTRACT

The emergence of newer SARS-CoV-2 variants recently reported in the UK, South Africa, and Brazil is a matter of great concern. The mutations mainly in the spike protein are the culprit behind the sudden rise in the infectivity and transmission of these variants. The scientific efforts provided us with few effective vaccines like Pfizer and Moderna, however the same needs to be re-investigated in the SARS-CoV-2 variants infected patients. This brief review, focuses on the emergence, how the variants originated and are geographically distributed around the world, which will make the researcher aware of the current pandemic situation

Keywords: SARS-CoV-2; B.1.1.7; Spike protein; Furin; Receptor Binding domain; ACE-2

INTRODUCTION

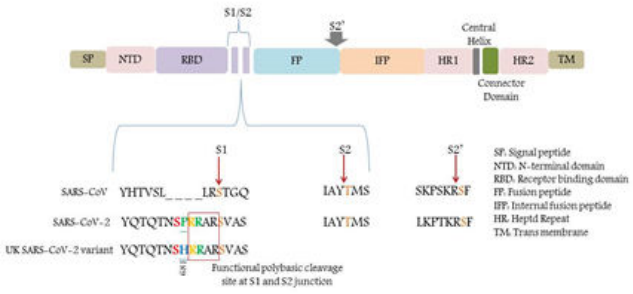
Since the emergence of the first case of SARS-CoV-2 within Wuhan province, more than 105 million COVID-19 cases with over 2.3 million deaths have been reported from 218 countries across the world (1). SARS-CoV-2 possessing spike protein is widely accepted for high infectivity and disease severity. Soon after it emerged from the possible bat/pangolins origin, its successful adoption of human to human and community transmission in diverse geographical regions remained its success story of pandemicity (2) (3).

During the initial months of the pandemic, the dominance of D614G variant with higher transmission efficiency has been deserved in the European countries (4). The reporting of recently SARS-CoV-2 variants in mink from the Netherland is also a matter of great concern. The independent evolution of novel B.1.1.7 variants from the United Kingdom and 501.Y.V2 mutant from South Africa have significantly alarmed the scientific community and raising serious concerns (5). The conformational changes in the spike protein due to D614G mutation in earlier variants and the recent B.1.1.7 variants possibly facilitated SARS-CoV-2 not only with high infectivity and transmissibility but also with immune evasion within the host.

Structural Relevance of Spike Protein

Following the binding of spike glycoprotein to the cell surface ACE2 receptor, SARS-CoV-2 enters into the endosomes. It is composed of S1 and S2 domains where, S1 domain contains a signal peptide, N-terminal domain, and Receptor-binding domain (RBD, 438-506 a.a.), help in the recognition of the human ACE2 receptors (6) (Figure 1).

Figure 1. Diagrammatic representation of spike glycoprotein showing S1 and S2 domain, where S1 contains NTD and RBD and S2 contains FP, IFP, HR1, and HR2. Polybasic cleavage site at the interface of S1/S2 contains the RRAR amino acid sequence which is the unique feature of SARS-CoV-2



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SARS-CoV-2 RBD has a high binding affinity through the receptor-binding site (RBS) i.e. GVEG (482-485 a.a.). The S2 subunit comprises two heptad repeat regions. The S1/S2 interface, a functional polybasic furin cleavage site (PRRARS'V), facilitates the virus's entry into the respiratory epithelial cells (7). Insertion of proline at the leading site created a turn facilitating the addition of three O-linked glycans around the cleavage sites at S673, T678, and S686 positions. Furin is a calcium-dependent membrane-bound protease expressed as 794 a. a. zymogen (8). RBD domain usually resonates between standing and lying-down positions. The former facilitates receptor binding and high infectivity whereas the latter position helps in immune evasion. The O-linked glycans further add on to the process of immune-evasion by creating a mucin-like domain protecting the key residues on spike protein.

Following infection, the spike protein binds to the hACE2 receptors for internalization and induces a change in the conformation of the protein. Dissociation of S1 by TMPRSS2 serine proteases facilitates fusion of viral envelope with the cell membrane of a host (7). Interestingly, the RBD domain in SARS-CoV-2 remains in a lying-down position, favoring immune-evasion and high infectivity.

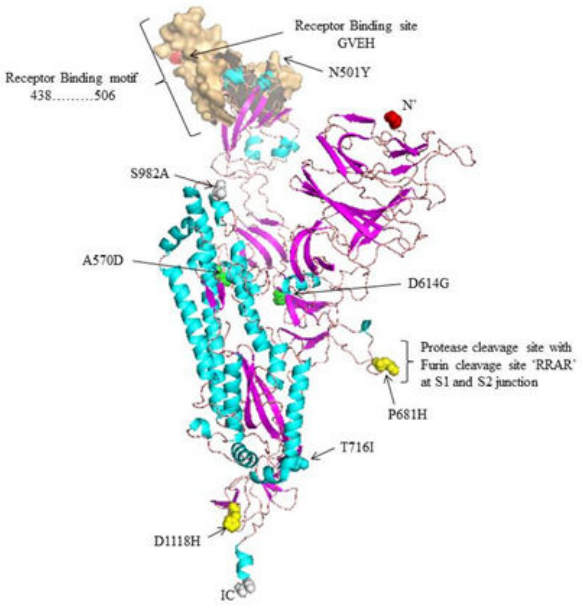
Circulation of D614G Variants

During the initial phase of the COVID-19 pandemic during June 2020, D614G (Aspartic-Glycine) mutation became more dominating impart higher transmissibility along with fitness advantage. The possible reason could be the higher percentage of an open configuration of RBD in the G614G strains resulted in a higher ability to bind to ACE-2. The microsecond all-atom simulation studies revealed favorable infection-capable open states of RBD in D614G variant, where reduced tensile hydrogen bonds, seem to favor the spike and hACE-2 receptors interaction (9). Cryo-electron microscopy of the trimeric spike protein revealed the D614G open-state configuration abolishing the hydrogen-bond interaction with T859 destabilizing the spike trimer and increase interaction between RBD and ACE2 (4). The D614G variant of the virus showed faster transmission and higher infectivity. Besides, experimentally it has displayed enhanced competitive fitness when inoculated in primary airway human epithelial cells and animal models (transgenic mice and hamsters) (10)

New Emerging SARS-CoV-2 UK Variants

As mutations are common with RNA viruses, 17 new mutations with high frequencies have been reported in UK strains by December 2020. First detected in mid-September, the variant has become a matter of concern on December 14, as high transmissibility by 60% is evidenced of all the recent infections. Molecular clock estimates showed nucleotide mutations at the rate of two changes per month, with an increase in reproductive number (Ro) by 0.4 (11). UK has suddenly emerged as a hot spot for the highly virulent variant of novel SARS-CoV-2, the B.1.1.7 variant (SARS-CoV-2 VOC-202012/01) resulting in a sudden surge in the COVID-19 positivity and hospitalization. The variant belonged to the clade GR and lineage B.1.1.7. Mathematical modelling revealed 56% high transmissibility than the other strains (12). Of all the 23 mutations acquired, 6 are synonymous, 3 are deletions, and 14 are non-synonymous mutations (Figure 2).

Figure 2. Structural representation of Spike protein showing major mutations in the B.1.1.7 variant. N501Y mutation occurs in the receptor-binding motif-containing receptor binding site which is crucial for binding with the hACE-2 receptor. D614G is the dominant substitution possibly responsible for high infectivity. P681H is important due to its placement next to the furin cleavage site 'RRAR at S1/S2 junction'. Other important mutations in the spike protein are S982A, A570D, D1118H, and T716I.



Among eight mutations in the spike gene, three are crucial and clinically relevant. The most important is the substitution of H with P at the highly variable S1/S2 furin cleavage site, position 681 (P681H), thereby altering the cleavage site and transmissibility. Interestingly SARS-CoV-1 lacks this mutation. The N501Y mutation in the RBD enhances the tight binding of spike protein with the hACE2 receptor at the entry point (13). Double deletion in the N terminal domain at 69-70, imparts a conformational change in the spike protein, possibly increasing the infectivity and/or immune evasion in immunocompromised patients (14) (15).

As of January 9, 2021, the existence of B.1.1.7 lineage is not only restricted to the United Kingdom (9504 sequences) but spread in 28 nations worldwide (9896 sequences) affecting Denmark, Ireland, Netherlands, Portugal, Israel, Italy, Australia, Finland, France, Sweden, USA, Slovakia, Singapore, Spain, Switzerland, New Zealand, Norway, Germany, Brazil, Jamaica, South Korea, India, Luxembourg, Hong Kong, Pakistan, Canada, Oman, and Lebanon (16).

South African Variant

In South Africa, a separate lineage of SARS-CoV-2 from the UK variant (clade GR) having N501Y mutation in the spike gene has

emerged independently and identified as 501Y.V2 or B.1.351 variant (17) (Pond et al., 2020). The variant 501.V2 (clade GH) might be more transmissible than the UK variant. The South African variant is documented to have more transmitted among the young population and more contagious than the prevalent A2a strain.

The 501.V2 variant has 8 lineage-defining mutations in the spike protein, of which 3 are in the RBD domain i.e. K417N, E484K, and N501Y (18). Extensive phylogenetic analysis of more than 190 sequences from this monophyletic cluster in South Africa suggested the emergence of this variant in early August 2020. In addition to D614G, non-synonymous mutations in the RBD (E484K, N501Y, K417N); NTD (L18F, D80A, D215G, R246I), and in loop 2 (A701V) of the spike protein are observed in clinical isolates of SARS-CoV-2. E484K, N501Y substitutions in the RBM forms the interface with the human ACE2 receptor. N501 forms part of the binding loop in the contact region of ACE2, forming a hydrogen bond with Y41 and also stabilizes K353 on hACE2 (19). E484 interacts with the K31 residue whereas K417 forms a salt bridge interaction across the central contact region with D30 of hACE2 and enhances binding affinity (20). Till January 20, 2021, 16 countries had been reported this lineage (555 sequences) are South Africa with the highest (447 sequences), followed by United Kingdom, Botswana, Ireland, Switzerland, Australia, France, Finland, Netherlands, South Korea, and Sweden.

The possible reason for the emergence of African lineage could be the evolution of the strain within the immunocompromised individual with prolonged viral infection as HIV infection is dominant in South Africa (16).

Mink Variants or Danish Cluster 5

A new SARS-CoV-2 variant detected in farmed mink in the Netherlands has the potential of transmission of mutations back to humans. This variant is defined by 4 mutations i.e. 69-70 deletions and replacement of 3 amino acids at Y453F, I692V, and M1229I in the spike protein (21). So far only 12 people in Denmark reported these 4 mutations. I692V and M1229I mutations are localized far away from the RBM, therefore, are not significant; however, Y453F mutation is anticipated to have a significant effect on viral infectivity or antibody susceptibility due to its presence in the RBM. This Y453F mutation may increase the affinity of spike protein for human ACE2 receptors, and possibly infect mink (22).

Recently Identified Brazilian Variant, Japanese Variant, and Others

Recently, Brazil identified with P.1 lineage with biological significant variants having K417T, E484K, and N501Y mutations in the Spike gene. In addition to Brazil with 29 sequences of this variant, Japan and South Korea reported 4 and 1 sequences respectively.

Japan identified a new SARS-CoV-2 variant which belonged to B.1.1.248 lineage in 4 Brazil returned travellers (23). This variant has 12 mutations including N501Y and E484K as observed in B. 1.1.7 and 501Y.V2 variants (24). E484K variant associated with escape from neutralizing antibodies was reported in the first distinct SARS-CoV-2 lineage reinfection case from Brazil (25). Owing to similarity with the 501Y.V2 variant, this lineage may be associated with increased infectivity and has been predicted to affect antibody neutralization (26).

Besides, receptor binding mutations in GR clade from Melbourne, GH clusters from Central Europe (S477N), and G clade variants from UK (N439K) are also relevant and need to be critically analysed. N440K variant of SARS-CoV-2 first reported in July 2020 from Andhra Pradesh is an immune-escape variant, which evades neutralizing Ab, thus infect people previously infected with another variant of SARS-CoV-2. A3i originated in east Singapore, Philippines, and presently replaced by clade A2a which has become a globally dominant clade including India (26).

Theories behind Evolution of Variants

Development of immune evasion mechanism in a prolonged SARS-CoV-2 infected immunocompromised patient may lead to a high accumulation of immune escape mutants, thereby facilitated the emergence of highly infective variants (27). Adaptive evolution in the virus and adaptation of the virus from animal to humans and back could be the other possible mechanism as seen in Mink and Mink-associated SARS-CoV-2 infection in humans reported from Denmark and Netherlands (28).

COVID-19 scenario in India

In India so far 10 million cases of COVID-19 with 151,364 deaths were reported (1). Recently, with the efforts of 10 premier research institutes of India under the initiative of DBT, the Indian SARS-CoV-2 Genomics Consortium (INSACOG) identified 71 cases with the new UK COVID-19 strains. So far of the 10,787 samples tested, 736 belong to the UK variant, 34 of the South Africa and 1 brazillian variant. The double mutations at E484Q and L452R may confer immune escape and incrased infectivity. Further efforts are on to trace the new emergent strains and the measures to restrict their speed.

Major Concern and Future Prospective

As a result of tireless and collaborative efforts of scientists and the involvement of huge finance around the world, we have two FDA-approved mRNA vaccines for Emergency Use i.e. Pfizer-BioNTech BNT162b2 mRNA and Moderna's mRNA-1273 COVID-19 vaccines (29)(30). The major issue is the supply of mRNA vaccine under low temperature for storage and transport.

With the higher transmission rate of SARS-CoV-2, the chances to mutate increases, therefore limiting the spread is crucial to limit the mutation, thereby easier to control the pandemic. Whole-genome sequencing and identification of variants on a large scale could be the strategic step to trace the phylodynamics of SARS-CoV-2 mutants' transmission. Although COVID-19 vaccines for human use on an emergency basis are in the market; still wearing a mask, social distancing and frequent hand washing remain the prime preventive options.

Author statements

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The author(s) declare that there is no conflict of interest

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