SARS-CoV-2 Variants

Subjects: Infectious Diseases

Contributor: Mariano Esteban , Carmen Elena Gomez

The emergence of SARS-CoV-2 variants have significantly impact the course of COVID-19 pandemic worldwide. They have in common a higher transmissibility, becoming dominant within populations in a short time, and an accumulation of a high number of mutations in the spike (S) protein, especially within the amino terminal domain (NTD) and the receptor binding domain (RBD) which could affect the efficacy of the current licenced vaccines.

SARS-CoV-2 COVID-19 variant

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causal agent of the worldwide coronavirus disease 2019 (COVID-19) pandemic, which is causing major health as well as social and economic burden with unprecedented consequences. Records show 150 million infection cases worldwide with a global death of 3.1 million people late April 2021. At the beginning of the SARS-CoV-2 pandemic, there were only modest levels of genetic evolution mainly because of two factors: (i) the global absence of immunity against this new pathogen; and (ii) the low mutation rates of the coronaviruses which encode an enzyme with proofreading function that increases the fidelity of the replication process [1]. In early March 2020, a new variant was detected with a single D614G mutation in the spike (S) glycoprotein of SARS-CoV-2 that spread to global dominance over the next month due to increased transmissibility and virus replication [2][3]. Since December 2020, novel SARS-CoV-2 variants that accumulate a high number of mutations, mainly in the S protein, have been detected in some geographical regions. These variants have been considered by the World Health Organization (WHO) as variants of concern (VOC) because of their potential risk to human health. The changes observed in the viral mutation rate during the course of the pandemic indicate a tendency towards a rapid antigenic variation and, hence, it is important to strengthen surveillance systems to control the emergence and the dissemination of new variants, looking over their impact on disease transmission and severity and on the efficacy of vaccines and treatments used globally.

2. Other Variants of Interest

The United States is the country with the highest incidence rates of COVID-19, and different states have reported the prevalence of all the emergent variants of concern. However, the expansion of a novel variant descended from cluster 20C and designated CAL.20C (20C/S:452R or B.1.429) has been reported in Southern California [4]. CAL.20C variant was first observed in July 2020 in one of 1247 samples from Los Angeles County and was not detected in Southern California again until October. Since then, the prevalence of this variant has increased, and, in January 2021, it accounted for 35% and 44% (37 of 85) of all samples collected in California state and Southern

California, respectively. However, relatively few samples have been sequenced, and sequencing is not performed uniformly throughout the state, making it difficult to establish a more accurate estimate of the expansion of this variant [5]. CAL.20C variant is defined by five mutations (ORF1a: I4205V; ORF1b: D1183Y; S: S13I, W152C, and L452R). In particular, the L452R mutation in the spike protein has been found to be resistant to certain therapeutic monoclonal antibodies [6]. As clinical outcomes have yet to be established, the functional effect of CAL.20C variant regarding infectivity and disease severity remains uncertain.

Another new coronavirus variant, named A.23.1, has been detected in Uganda and has quickly become the most common coronavirus in Uganda's capital city, Kampala. The set of the spike mutations in A.23.1 includes R102I, F157L, V367F, Q613H, and P681R. Additional substitutions in non-spike regions include non-structural protein (nsp) 3: E95K; nsp6: M86I and L98F; ORF8: L84S and E92K, and N: S202N and Q418H. As of 16 February 2021, 274 sequences of A.23.1 lineage have been detected in 17 countries [7]. In addition, an emerging lineage (now designated as B.1.526) of viral isolates in the New York region that shares mutations with previously reported variants has been recently detected by West et al. using a tool to query the spike mutational landscape. The most common sets of spike mutations in B.1.526 are L5F, T95I, D253G, and E484K or S477N, D614G, and A701V. This lineage appeared in late November 2020, and it accounts for ~5% of coronavirus genomes sequenced and was deposited in Global Initiative on Sharing Avian Influenza Data (GISAID) during late January 2021 [8]. Although the clinical impact of the A.23.1 and the B.1.526 variants is not yet clear, it is essential to perform a careful monitoring of these variants as well as a rapid assessment of the consequences of the spike protein changes for vaccine efficacy.

The UK has strengthened genomic surveillance to evaluate the molecular evolution of the prevalent B.1.1.7 variant. New variants with different substitutions have emerged as a consequence of both the high replication rates of the virus and the increasing selection pressure resulting from the growth of the seroprevalent fraction of the population of England. The ones that worry the most are L18F and E484K. The introduction of the L18F mutation confers a replicative advantage to the virus [9], whereas E484K mutation could confer resistance to immunity. Moreover, other non-B.1.1.7 lineages with the E484K mutation have been identified in some UK regions such as the VUI 202102/01 (A.23.1 with E484K) or the B.1.525 (VUI 2021 02/03) with 4 mutations within the spike protein (Q52R, E484K, Q677H, and F888L). Further work is needed to establish the impact of these mutations on protective vaccines efficacy in the context of the evolving variants that have acquired E484K mutation [10].

There is substantial variability in the course of COVID-19, ranging from asymptomatic infection to death. One of the main topics of ongoing research is how the emergence of the new SARS-CoV-2 variants impacts patient's outcome. However, there are no consistent data published yet, in part due to the fact that most of the genome sequences shared are not linked to clinical outcomes. One study performed by researchers from the University of Washington comparing two dominant clades of virus in circulation showed no significant difference in outcomes of hospitalization or death between clades [11]. Similarly, clinicians and scientists working in the frontline in South Africa have not observed any differences in symptoms in people infected with the new variant P.1.351, compared with people infected with other variants [12]. Nevertheless, further analysis is necessary to screen differences in COVID-19 symptom type, severity, or duration of the disease caused by the new VOC.

3. Population Monitoring of Variant by Genomic Sequencing

Worldwide expansion of genomic sequencing and data exchange is essential to detect the emergence of new variants or their introduction in a given country or region. To date, more than 528,000 sequences have been submitted to the GISAID that promotes the rapid sharing of data from the coronavirus causing COVID-19; however, most of them come from only a few countries. It is necessary that all the countries share sequence information to understand the spread of SARS-CoV-2. Improving the geographical coverage of sequencing is essential for the world to adequately capture the viral changes and establish alternative measures, as previously reported in Netherlands [13]. Increased sequencing capacity is a priority research area for the WHO. In order to achieve this objective, a number of recommendations have been established highlighting the need to have or implement a network of laboratories with sequencing experience integrated within the epidemiological surveillance system to generate useful information for the decision-making of public health measures and to ensure that resources are available to manage increasing numbers of COVID-19 detection and characterization of sample requests.

4. Defining SARS-CoV-2 Variants More Resistant to Vaccine Action

There are several lines of action to establish the role played by the mutations introduced into the SARS-CoV-2 genome on resistance to the action of the immune responses induced by current vaccines mostly targeting the spike protein. To this end, the scientific community, WHO, and companies have warned of the need to experimentally establish assays that determine to what extent the various variants already identified and those upcoming, that are spreading in the population, are due to mutational changes that confer an enhanced degree of resistance to the antibodies generated in infected or vaccinated people. Experimental approaches to be followed are: (1) demonstration in experimental animal models (humanized mice susceptible to virus, hamsters, ferrets, and macaques) that emerging variants are more virulent (higher transmission, replication, organ damage, morbidity, and mortality) than Wuhan's reference strain; (2) demonstration that these variants withstand the neutralizing action of immune sera induced in current vaccination campaigns, such as mRNA-based vaccines (Pfizer, Moderna), non-replicating adenovirus-based vaccines (AstraZeneca, Janssen, Sputnik), protein subunit (Novavax), inactivated virus (Sinovac), and others; and (3) demonstration of the degree of variant control in vaccinated personnel in comparison with infection by the parental Wuhan strain

In those cases in which increased resistance to antibodies was demonstrated, as indicated by the above experimental data, it should also be confirmed that T cell responses are also affected, or if, on the contrary, the controlling effect of the infection by T lymphocytes is maintained. These experimental data in animals and humans are necessary to establish the highest sensitivity and resistance of the different variants to the immune action.

The reduction in the efficacy of different vaccine candidates in regions where the variants of concern have become prevalent has accelerated the decision of many of the companies that produce current COVID-19 vaccines to consider modifying their designs to cover circulating viral variants. The immediate consequence is that there should be on the market new vaccines from the same production companies, which could be given either to those people

already vaccinated as a recall dose or to those who have not yet received the vaccine dose. These new vaccines modified in their specific platforms would entail additional costs and could in turn lead to more resistant variants with additional mutations due to selective pressure from the immune system. We hope this does not occur, but we must remain vigilant about the evolution.

Anything that can be done to suppress spread of SARS-CoV-2 will help to limit the emergence of new variants. However, other strategies that include multivalent designs focused on conserved regions of different viral proteins could be of great prophylactic relevance to counteract escape variants that are emerging. In this regard, a sustained effort to develop a pan-SARS-CoV-2 vaccine is warranted. Similarly, to improve the efficacy of the current treatments, it will be of relevance to use a combination of antibodies directed against other viral regions in addition to the spike protein or to implement the “lethal mutagenesis” strategy as alternatives that slow the viral diversification [14].

References

1. Denison, M.R.; Graham, R.L.; Donaldson, E.F.; Eckerle, L.D.; Baric, R.S. Coronaviruses: An RNA Proofreading Machine Regulates Replication Fidelity and Diversity. RNA Biol. 2011, 8, 270–279.
2. Korber, B.; Fischer, W.M.; Gnanakaran, S.; Yoon, H.; Theiler, J.; Abfalterer, W.; Hengartner, N.; Giorgi, E.E.; Bhattacharya, T.; Foley, B.; et al. Tracking Changes in SARS-CoV-2 Spike: Evidence That D614G Increases Infectivity of the COVID-19 Virus. Cell 2020, 182, 812–827.e19.
3. Hou, Y.J.; Chiba, S.; Halfmann, P.; Ehre, C.; Kuroda, M.; Dinnon, K.H.; Leist, S.R.; Schäfer, A.; Nakajima, N.; Takahashi, K.; et al. SARS-CoV-2 D614G Variant Exhibits Efficient Replication Ex Vivo and Transmission In Vivo. Science 2020, 370.
4. Available online: (accessed on 9 March 2021).
5. Zhang, W.; Davis, B.D.; Chen, S.S.; Sincuir Martinez, J.M.; Plummer, J.T.; Vail, E. Emergence of a Novel SARS-CoV-2 Variant in Southern California. JAMA 2021.
6. Li, Q.; Wu, J.; Nie, J.; Zhang, L.; Hao, H.; Liu, S.; Zhao, C.; Zhang, Q.; Liu, H.; Nie, L.; et al. The Impact of Mutations in SARS-CoV-2 Spike on Viral Infectivity and Antigenicity. Cell 2020, 182, 1284–1294.e9.
7. Bugembe, D.L.; Phan, M.V.T.; Ssewanyana, I.; Semanda, P.; Nansumba, H.; Dhaala, B.; Nabadda, S.; O’Toole, Á.N.; Rambaut, A.; Kaleebu, P.; et al. A SARS-CoV-2 Lineage A Variant (A.23.1) with Altered Spike Has Emerged and Is Dominating the Current Uganda Epidemic. medRxiv 2021.
8. West, A.P.; Barnes, C.O.; Yang, Z.; Bjorkman, P.J. SARS-CoV-2 Lineage B.1.526 Emerging in the New York Region Detected by Software Utility Created to Query the Spike Mutational Landscape.

bioRxiv 2021.

9. Grabowski, F.; Kochańczyk, M.; Lipniacki, T. L18F Substrain of SARS-CoV-2 VOC-202012/01 Is Rapidly Spreading in England. medRxiv 2021.
10. Investigation of Novel SARS-CoV-2 Variant—Variant of Concern; Public Health England: Birmingham, UK, 2021.
11. Nakamichi, K.; Shen, J.Z.; Lee, C.S.; Lee, A.; Roberts, E.A.; Simonson, P.D.; Roychoudhury, P.; Andriesen, J.; Randhawa, A.K.; Mathias, P.C.; et al. Hospitalization and Mortality Associated with SARS-CoV-2 Viral Clades in COVID-19. Sci. Rep. 2021, 11, 1–11.
12. de Oliveira, T.; Hanekom, W. South African Scientists Who Discovered New COVID-19 Variant Share What They Know. Available online: (accessed on 4 March 2021).
13. Oude Munnink, B.B.; Nieuwenhuijse, D.F.; Stein, M.; O'Toole, Á.; Haverkate, M.; Mollers, M.; Kamga, S.K.; Schapendonk, C.; Pronk, M.; Lexmond, P.; et al. Rapid SARS-CoV-2 Whole-Genome Sequencing and Analysis for Informed Public Health Decision-Making in the Netherlands. Nat. Med. 2020, 26, 1405–1410.
14. Shannon, A.; Selisko, B.; Le, N.-T.-T.; Huchting, J.; Touret, F.; Piorkowski, G.; Fattorini, V.; Ferron, F.; Decroly, E.; Meier, C.; et al. Rapid Incorporation of Favipiravir by the Fast and Permissive Viral RNA Polymerase Complex Results in SARS-CoV-2 Lethal Mutagenesis. Nat. Commun. 2020, 11, 4682.