Molecular Therapy
Nucleic Acids
Editorial

D614G mutation eventuates in all VOI and VOC in SARS-CoV-2: Is it part of the positive selection pioneered by Darwin?

Recently, several emerging variants of SARS-CoV-2 have originated from the Wuhan strain and spread throughout the globe within one and a half years. One mutation, D614G, is very prominent in all VOI and VOC in SARS-CoV-2. This mutation might help to increase the viral fitness in all emerging variants where the mutation is present. With the help of this mutation (D614G), the SARS-CoV-2 variants have gained viral fitness to enhance viral replication and increase transmission. This paper attempts to answer the question of whether the mutation (D614G) occurs due to positive selection or not.

Scientists are trying to characterize the coronavirus disease (COVID-19) in order to develop flawless therapeutic approaches to combat the global pandemic. This RNA virus belongs to the beta coronavirus group. Like other RNA viruses, it is expeditiously evolving and transmitting, and it has killed over 3.7 million people globally. During the rapid transmission, it is common to accrue various mutations in the pathogen's genetic structure, leading to the occurrence of more diverse and lethal forms. Especially for pathogenic viruses, decoding their evolutionary pathways will enable scientists to clarify and comprehend the precise pathogenesis or pathophysiology of the contagion. Such an approach will ultimately allow scientists to develop an effective line of treatment regimen either by creating potential vaccines or by discovering new drugs to keep the transmission in check.[1]

The RNA viruses such as the common cold, influenza, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 are inherently prone to mutations, and high rates of mutation would catalyze rapid evolution compared to their counterparts, the DNA viruses such as the herpesviruses, smallpox viruses, adenoviruses, and papillomaviruses. The faster mutation rate per se in viruses provide better prospects for natural selection to act upon instantly to perfectly shape and create distinct new strains. The vast majority of the RNA viruses that infect and kill humans tend to jump from animals.[2] It is imperative to note that natural selection plays both the proximate and ultimate role to shape the evolutionary trajectory of viruses, and hence it could be one of the deterministic influences to configure the radiation pathways of that particular pathogen.[1] During a viral pandemic, it was observed that natural selection favored some mutations over others and also played a deciding role in influencing their pathogenicity over time.[3]

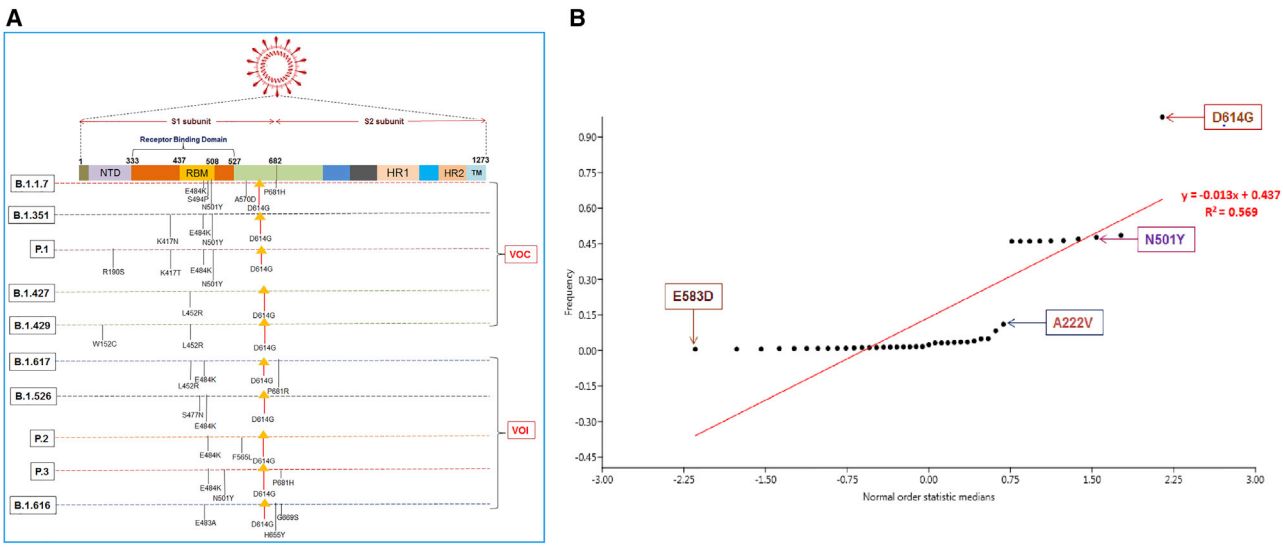

Figure 1. Significant features of D614G mutation gained through positive selection

All of the emerging VOC and VOI have gained the mutation, which is found in all the emerging variants. D614G mutation occurs in the highest frequency compared to other mutations. (A) The schematic diagram shows the D614G mutation in S-glycoprotein of all emerging variants of concern (VOC) and interest (VOI) of SARS-CoV-2. (B) A statistical model illustrates the comparison of the 43 mutations from all emerging VOC and VOI of SARS-CoV-2. The model shows D614G mutation as the predominant one with the highest frequency (0.0486). At the same time, the lowest frequency was noted in E583D mutation (0.0057). We used the open-source data of the mutation frequency of all 43 mutations from the Bacterial and Viral Bioinformatics Resource Center (BV-BRC) (https://bv-brc.org/).

Figure 2. D614G mutation eventuates in all VOI and VOC through positive selection and spread worldwide

This figure shows that the variants of SARS-CoV-2 with D614G mutation have spread in different parts of the United States. It also demonstrates the phylodynamics of the variants with D614G mutation from different parts of the United States. (A) Transmission pattern of the variants of SARS-CoV-2 with D614G mutation in Louisiana, USA. (B) Phylodynamics of the variants of SARS-CoV-2 with D614G mutation in Louisiana, USA. (C) Transmission pattern of the variants of SARS-CoV-2 with D614G mutation in Oregon, USA. (D) Phylodynamics of the variants of SARS-CoV-2 with D614G mutation in Oregon, USA. Map of the United States' transmission pattern with the variants of SARS-CoV-2 with D614G mutation and their phylodynamics of all area-specific variants showing D614G mutation circulating in all areas in the United States. Map of the transmission pattern of all regions and phylodynamics of all variants of a specific location was developed before July 7, 2021, using GISAID data.[18]

The SARS coronavirus 2 (SARS-CoV-2) virus infects the human cell by interacting with its spike protein on its surface where the angiotensin-converting-2 (ACE2) protein receptor presents in the cell.[4] The spike protein consists of three protomers, and when they interact with the ACE2 receptor, it promotes the entry of the virus into a host cell.[4] Thus, the spike protein has become a specific target for scientists to formulate therapeutic approaches, and therefore, the molecular structure of the spike protein has been characterized recently.[4,5] The chemistry of interaction between the spike protein and its receptor has also been explored.[6,7] Despite the fact that the rapid mutation rate is not all that unusual for RNA viruses like SARS-CoV-2, the outstanding concern is whether or not the mutated strains alter viral properties. A classic example is the D614G mutated variant of SARS-CoV-2 that has become so dominant in all variants of concern (VOC) and variants of interest (VOI) globally (Figure 1).[8]

Reports have confirmed the mutation of a particular SARS-CoV-2 variant at any geographical level and the distribution of that specific mutation occurring both regionally and globally (Figures 2 and 3).[9] This mutated variant has been transmitted worldwide with high infectious rate compared to its original counterpart (Figure 4).[9,10] It is therefore imperative to mention that higher viral loads in the upper respiratory tract of humans have been associated with the mutated variant, suggesting a particular alteration that increases the efficiency of the virus entering the host cell while boosting the binding affinity of spike protein to its cognate ACE2 receptor.[11] This particular mutated variant is dangerously communicable as it infects multiple human cell types.[12] Plante et al.[13] reported that the D614G mutation might alter the viral fitness of SARS-CoV-2. With the help of the mutation (D614G), the SARS-CoV-2 variants are gaining viral fitness to improve replication and increase transmission.

The natural selection favors some mutations over others, and a higher fitness advantage could be one of the reasons catalyzing the faster replication of a specific type. That is why the new mutant variant has become more infections with faster communicable potential compared to its ancestral form in terms of disease progression.[9] The expansion of a particular viral mutation is regulated by various evolutionary factors that include founder effect, population bottleneck, genetic drift, range expansion, population growth, and

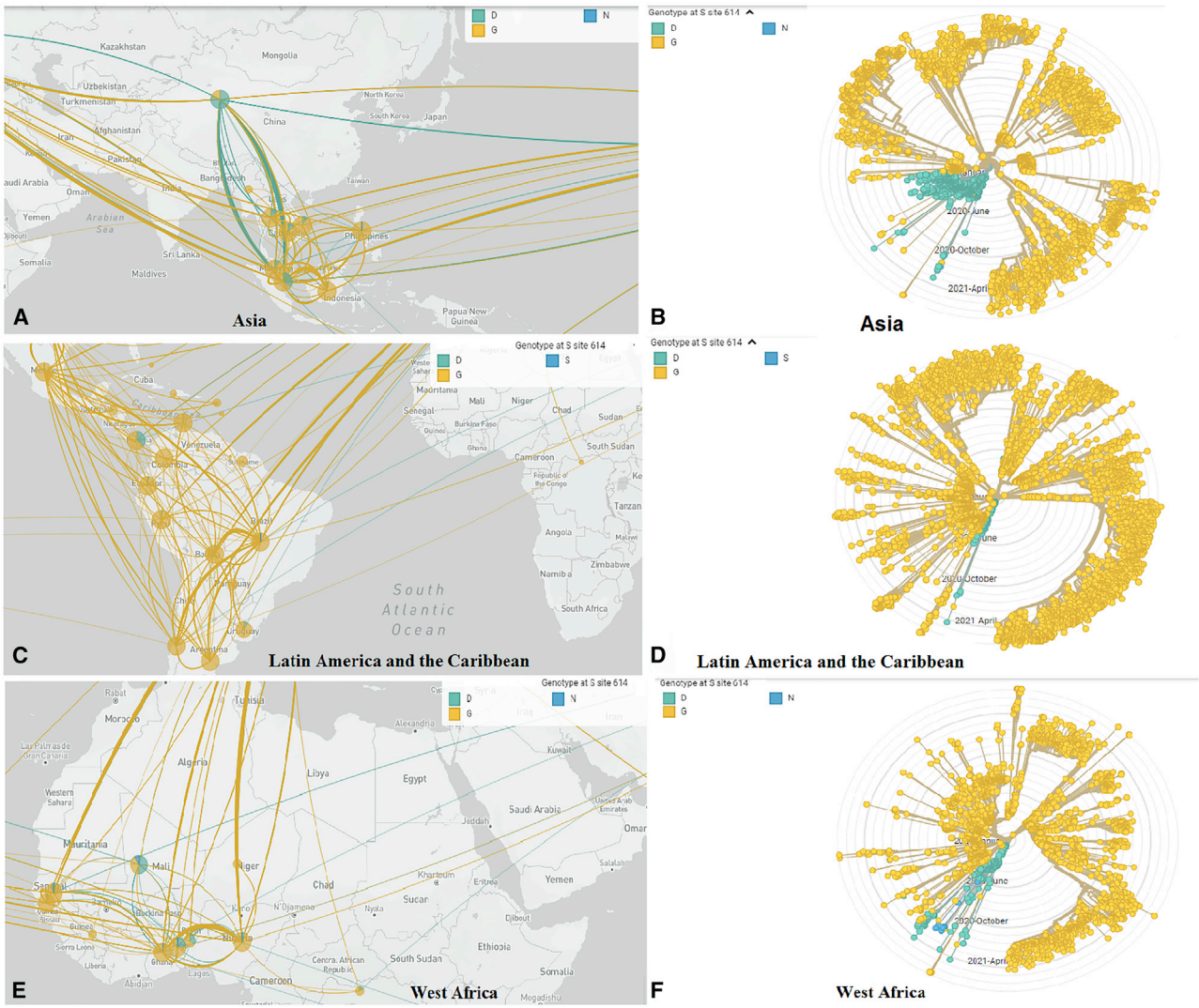

Figure 3. Through positive selection, D614G mutation emerges in all VOI and VOC and spreads worldwide

This figure shows that the variants of SARS-CoV-2 with D614G mutation have spread in different parts of the world other than the United States. It also shows the phylodynamics of the variants with D614G mutation in different parts of the world other than the United States. (A) The transmission pattern of the variants of SARS-CoV-2 with D614G mutation in Asia. (B) Phylodynamics of the variants of SARS-CoV-2 with D614G mutation in Asia. (C) Transmission pattern of the variants of SARS-CoV-2 with D614G mutation in Latin America and the Caribbean. (D) Phylodynamics of the variants of SARS-CoV-2 with D614G mutation in Latin America and the Caribbean. (E) Transmission pattern of the variants of SARS-CoV-2 with D614G mutation in West Africa. (F) Phylodynamics of the variants of SARS-CoV-2 with D614G mutation in West Africa. Map of the transmission pattern of all regions with the variants of SARS-CoV-2 with D614G mutation and their phylodynamics of all area-specific variants showing D614G mutation circulating worldwide. Map of the transmission pattern of all regions and phylodynamics of all variants of a specific area was developed before July 7, 2021, using GISAID data.[18]

ultimately natural selection. The variant with faster mutation capacity may persist in population for an extended period with a higher frequency as it is evolutionarily advantageous for the pathogen.[10]

Natural selection plays a pivotal role in removing deleterious short-lived viral variants from a population by imposing positive selection, which is the rule of thumb to shape the selection progression of viral replication and evolution.[14] Ideally, pathogenic microorganisms should opt for a reduced level of virulence in evolution since greater virulence associated with microscopic pathogens can lead to extinction not only of its host, but also for itself. Thus, natural selection favors the level of virulence maximizing the rate of increase in the pathogenic population to optimize the evolutionary trajectory by establishing a potential relationship between transmissibility and outcome of that particular virus on host

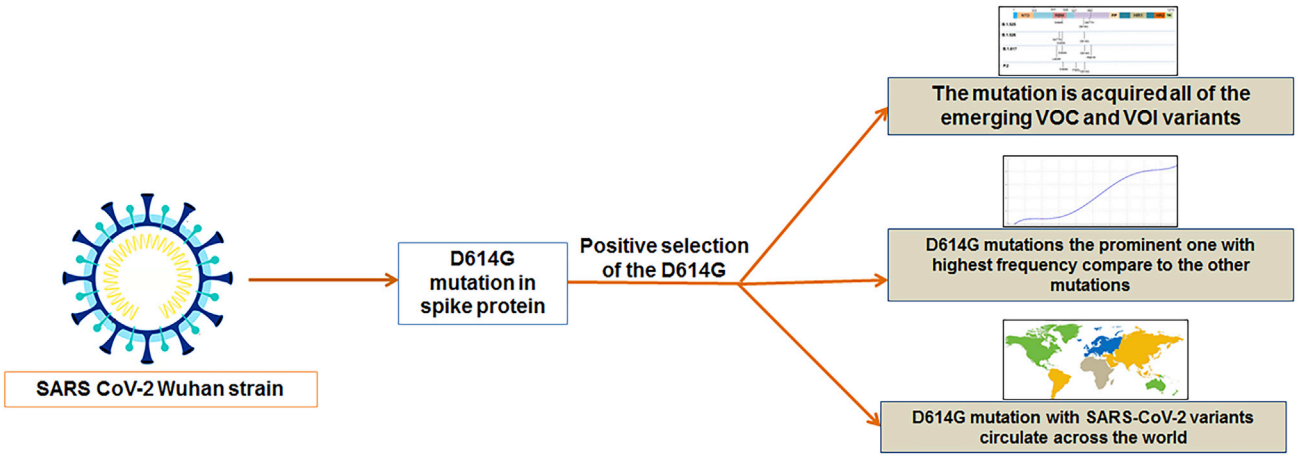

Figure 4. The hypothetical diagram illustrates the positive selection of the D614G mutation. From our previous analysis (Figures 1–3), finally, we have concluded by stating D614G mutation occurrence in all the emerging variants of concern (VOC) and interest (VOI) of SARS-CoV-2 with the highest frequency and circulating throughout the World.

mortality.[15] Trucchi et al.[16] proposed a hypothesis that the D614G variants got a selective advantage due to structural changes in the furin-like domain in S-glycoprotein. The mutation helps to change the conformational plasticity in this domain, which further helps to increase the volume of the cavity of this domain and its surrounding cleavage site in S-glycoprotein. This structural change favors the virus to interact with the host, and it appears to be the evolutionary strength of the virus.

It is well proven that positive selection is one of the foremost causes for molecular evolution. Some may consider that natural selection through random genetic drift could play a role in triggering an array of variants.[17] However, we conclude from our analysis that the D614G mutation is not at all a vibrant outcome of genetic drift, and instead, it appears to be part of positive selection. Thus, further exploration of D614G mutation will certainly contribute to better understanding of the molecular evolution of emerging variants of SARS-CoV-2.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

ACKNOWLEDGMENTS

We are thankful to Bacterial and Viral Bioinformatics Resource Center (BV-BRC) and GISAID database and their researcher who developed these web servers/databases.

AUTHOR CONTRIBUTIONS

Conceptualization, C.C.; Writing – Original Draft, C.C., A.S., and G.A.; Writing – Review and Editing, C.C., A.R.S., and M.B.; Validation and Formal Analysis, A.R.S. and M.B.; Supervision and Funding, S.-S.L. and C.C.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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https://doi.org/10.1016/j.omtn.2021.07.011

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