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Review of genetic variations in different generations of COVID-19

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Abstract

Significant genetic variances across generations of COVID-19 have resulted from the continuous evolution of the SARS-CoV-2 virus. The consequences of these differences on transmission, pathogenicity, and vaccination efficacy are investigated in this work. Public health reactions as well as the creation of sensible treatments and vaccines depend on an awareness of these genetic modifications. Several variants of concern resulting from the genetic variances in SARS-CoV-2 have surfaced with special traits that could affect the path of the epidemic. Transmissibility has revealed variations in these variants; some have spread faster than others, which would result in more cases and possible burden on healthcare systems. Furthermore, certain versions have shown alterations that can influence the capacity of the virus to avoid immunological reactions, therefore casting questions regarding the efficacy of current vaccinations. Our public health plans must change as we keep observing these genetic variations. Managing the effect of COVID-19 will depend critically on surveillance of viral changes in conjunction with continuous study on vaccine improvements. The knowledge gained from the genetic differences in SARS-CoV-2 will not only guide our reaction to this epidemic but also equip us for next infectious disease crises.

Keywords: COVID-19; Genetics; Generation; Vaccines; Variation

1. Introduction

SARS-CoV-2 is a novel human coronavirus that is the causative agent of COVID-19, first identified in December 2019 in Wuhan, the capital of China's Hubei province, and has since spread globally into a pandemic [1]. This is a positive sense single stranded RNA virus (Subtype: Betacoronavirus 2b) that has a relatively slow mutation rate compared to other RNA viruses. This mutation rate is estimated to be around 3x10-5 substitutions per site per year based on a study of three distinct SARS-CoV-2 genomes from China that estimated the three genomes to last shared a common ancestor in November or December 2019. This study found that SARS-CoV-2 has a similar substitution rate to other coronavirus viruses. Mutation is the change in the sequence of genetic material and happens as a mistake when genetic material (in SARS-CoV-2's case, RNA) is being copied. These mutations happen to the virus's genome (all of its genetic material) and can cause changes in the protein structure of a virus, can lead to a gain or loss of a function of a particular gene, or it may have no effect at all. These mutations cause the virus to have a genetic variation. Genetic variation refers to the variation in the nucleotides, genes, chromosomes, or genome structure that is passed from parents to offspring. This can be caused by a number of different factors, such as mutation, gene flow, and sexual reproduction. SARS-CoV-2 has been introduced to many different populations that introduced the factor of gene flow, leading to genetic differences on a global scale. Given the current understanding of the transmission to SARS-CoV-2, the virus is transmitted via respiratory droplets from person to person. This means that person- to-person contact is an effective way for the virus

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to spread. Sexual reproduction is a significant factor in the spread of SARS-CoV-2, as it has been recorded to have infected people of all ages and both genders. These people who are infected may go on to reproduce and spread their genetic variation of SARS-CoV-2 to the next generation. All of these factors that contribute to the genetic variation of SARS-CoV-2 are crucial when attempting to understand the current and future effects of this virus, usually in comparison with other viruses or past strains of coronavirus [2-4].

2. Overview of COVID-19

Covid-19 is an infectious disease caused by a virus strain SARS-CoV-2. It was first identified in December 2019 in Wuhan, China, and has since spread globally, resulting in an ongoing pandemic [5].Covid-19 presents with a wide range of symptoms. The most common include fever, dry cough and tiredness. Other symptoms include shortness of breath, aches and pains, sore throat and very few people will report diarrhea, nausea or a runny nose [6]. Symptoms begin gradually and are usually mild, and some people can become infected but only have very mild symptoms. Most people (about 80%) recover from the disease without needing hospital treatment. Around 1 person in 6 becomes seriously ill and develops difficulty breathing. Older people, and those with underlying medical problems like high blood pressure, heart and lung problems, diabetes, or cancer, are at higher risk of developing serious illness. However, anyone can catch Covid-19 and become seriously ill. A smaller proportion of the people who catch Covid-19 develop severe pneumonia. The disease is more serious in those over 80 years old, and in those with other health conditions [7].

2.1. Importance of Genetic Variations

Variations in an organism's DNA, from individuals to populations to entire species, are fundamental to the action of natural selection and evolution. Covid-19 has spread across the world, leading to varying viral genomes and the emergence of genetic [8]. This importance of genetic mutations within the SARS-CoV-2 virus can have a number of impacts, from altering the transmissibility of the virus, increasing the severity of Covid-19, evading immune responses, preventing detection of the virus or having no impact at all. Some of these changes can be detrimental, others can be beneficial for the virus's survival and future generations, others can be unimportant or have no effect on the virus. This section should explore the importance of genetic variations occurring in SARS-CoV-2 throughout the Covid-19 pandemic, from a global standpoint [9].

2.2. First Generation Variations

SARS-CoV-2 has undergone mutations that have had a major influence on pathogenesis during the COVID-19 pandemic. The most important concern about different SARS-CoV-2 variants is the risky changes that could worsen the severity of the disease or reduce the effects of vaccines [10]. Any living organism with cells has a gene sequence that is unique to that organism. A genetic variant is a differing gene sequence compared to a standard known sequence. Variants are often caused by mutations to the DNA. This essay is focused around the reference sequence WuhCor1 of a SARS-CoV-2 virus [11]. This essay is an exploration of the genetic mutations of SARS-CoV-2 viruses, which are the cause of COVID-19 viral illness. This essay also explores the clinical implications of these mutations. To prevent ambiguity, the term "strain" is not used in this essay as the author agreed with experts that a SARS-CoV-2 virus is considered as mutating viruses with said mutations being tracked. A mutation is a change in the sequence of genetic material. Mutations to the genetic material can create new strains of a virus. This essay describes genetic mutations by how they appear on a gene sequence. A gene sequence is a consecutive and fixed order of nucleotides along a DNA [12].

2.3. Identification of Initial Genetic Variants

Early in the pandemic, there was no available SARS-CoV-2 genomic data as it had not yet occurred or the data was difficult to gain access to [13]. It is also at this point where the strain of the virus was relatively consistent across locations. As lockdowns occurred and the virus spread globally, the potential for genomic sequencing as a surveillance method became more evident. This meant that as the pandemic continued, an increasing number of sequences were made publicly available to aid in understanding changes in the virus' genome. The first large effort to standardize and share SARS-CoV-2 genomic data was through the establishment of the Nextstrain (nextstrain.org) and GISAID (platform.gisaid.org) platforms. By compiling data from around the world, Nextstrain and GISAID have facilitated tracking global transmission pathways between geographic regions and determining when and where the virus has accumulated specific mutations. This also enables a genealogy of the virus to be constructed and subsequently helps in understanding if specific viral strains are dying out or becoming more prevalent [14].

2.4. Impact of First-Generation Variations on Transmission

Mutations in SARS-CoV-2 are poorly understood, but evidence is emerging. A study used global data to establish genetic types of the virus. It revealed two major types: L and S. The L type was more infectious. 14 mutations were identified in

the spike glycoprotein, with six leading to changes in amino acids. One mutation, D614G, resulted in increased transmissibility. These results could inform antiviral treatments and vaccines. The L type is associated with higher virus load and increased frequency of the G614 strain, indicating higher transmission rates and implications for public health [15].

2.5. Clinical Implications of First-Generation Variations

Through its distinct clinical phases, COVID-19 disease has demonstrated variety in its presentations, likely in part due to the virus's genetic variations. Some of the genetic variants of the virus can cause milder symptoms. While others can cause more severe disease [16]. The initial SARS-CoV-2 viruses had a unique mutation leading to the D614G variant. The D614G variant later became the globally dominant form of the virus because it had a higher transmission rate than the original virus [17].

Additionally, the D614G variant was associated with higher viral loads in the upper respiratory tract of patients, although this did not lead to more severe disease outcomes compared to the original virus. Several studies have shown that patients infected with the D614G variant have higher viral loads in their upper respiratory tracts compared to patients infected with the original virus type [18]. Increased viral load is associated with higher transmission rates; thus, it is expected that the D614G variant is more transmissible than the original virus type. The D614G variant is of particular interest because one of the goals of COVID-19 vaccines is to elicit an immune response that protects against SARS-CoV-2 infection and disease. Data from in vitro studies and studies in hamsters have shown that vaccine-induced immune responses are effective in protecting against the D614G variant [19]. However, This does not rule out the possibility of the emergence of other variants that escape immunity from prior infection or vaccination [20]. Other genetic variations of the virus have implications for COVID-19 therapeutics [21]. An example is a preliminary report that identified a SARS-CoV-2 variant with a 382- nucleotide deletion (D614Δ) that had emerged in Singapore in August 2020 and is associated with increased immune escape as compared to the commonly occurring D614G variant. Patients infected with the D614Δ variant were more likely to require oxygen supplementation and had higher respiratory rates. This variant is of concern because it may reduce the efficacy of certain therapeutic agents [21].

3. Second Generation Variations

The emergence of new genetic variants Nucleotide substitution is the most common type of mutation in the genome of RNA viruses. As with all RNA viruses, SARS-CoV-2 acquires mutations in its genome at a faster rate than DNA viruses [22]. Studies by the COVID-19 Genomics UK (COG-UK) consortium have identified several thousand variants in the genomes of SARS-CoV-2. Most of these variants are neutral or deleterious to the virus and therefore have little to no impact on the phenotype of the virus (Ashford F, Best A, Dunn SJ et all 2022). However, some variants will have effects on the virus. Perhaps the most easily understood variant to date is the D614G variant in the gene encoding the spike protein. This variant rapidly became the globally dominant form of SARS-CoV-2, and although there was no clear evidence to suggest it had altered the transmissibility, it was inferred to have some effect on fitness. The D614G mutated virus was more resistant to neutralizing antibodies, and while it did not cause a higher number of infections, infected patients had a higher viral load. This suggested that the mutation had increased the stability of the virion. So, in effect, the mutation facilitated the virus to be a more efficient pathogen [22]. As of January 2022, there have only been a few reported instances of human infection with a second-generation lineage of SARS-CoV-2. The emergence of these variants is, however, unsurprising. In simple terms, the virus is continually being copied and there is constant production of new viral genomes. Although high-fidelity replication is a feature of coronaviruses, the large number of transmissions in the global population means that mutations can occur frequently and can be acted upon by natural selection [23].

3.1. Emergence of New Genetic Variants

The SARS-CoV-2 virus is an RNA virus, meaning it has a very high mutation rate. With the scale of transmission that has occurred over, it is very likely that multiple variants of the virus have emerged [24]. Having a large number of people infected with the virus increases the chances of viral mutation and recombination, as the virus is replicating within a large population of infected people [24]. Although most mutations that occur in viruses like SARS-CoV-2 are neutral (having no effect) or deleterious (reducing the replication of the virus), it is possible that some of the mutations have allowed the virus to be more transmissible between people, and in some cases, it may allow the virus to avoid the host's immune response and cause repeat infection. As a result of natural selection, these new mutant viruses may outcompete the original strain of SARS-CoV-2, resulting in a second generation of the virus with different genetic variations [25].

3.2. Spread and Transmissibility of Second-Generation Variations

One of the most important factors in the spread of SARS-CoV-2 is when infected people are most likely to transmit the virus to others. As an acute infection, the amount of virus shed by infected persons varies over the course of the infection. Peak transmissibility of SARS-CoV has been associated with the onset of symptoms as shedding of virus is at its highest levels in the second week of illness [26]. Asymptomatic infections have been reported and in these cases it is unclear when these persons are most infectious. Close contacts of known cases who have been identified through contact tracing studies are at the highest risk of infection [27]. Healthcare workers have also been identified as a high risk group due to their exposure to patients with SARS. It is known that a significant proportion of individuals acquire infection within hospital settings. This pattern of nosocomial infection was also observed during the SARS pandemic and indicates the importance of effective infection control to prevent spread of SARS-CoV. Variable patterns of spread and transmission have been observed between different countries [27]. Identification of SARS-CoV-2 in stool specimens as well as the demonstration of live virus in stool culture indicates that faeco-oral transmission is possible [27]. Better understanding of the modes of transmission and groups at highest risk of infection for SARS-CoV-2 will enable targeted control measures to prevent and limit spread of infection. These measures will be essential in reducing the global impact of COVID-19 and may prevent future spread of SARS-CoV-2 in the event of re- emergence [28].

3.3. Effects of Second-Generation Variations on Disease Severity

Recently, a study using COVID-19 patients from multiple countries has identified several viral genetic variants that might affect disease severity. This study is done by a statistical analysis to associate individual viral gene mutations with disease severity, clinical, and patient-reported outcomes of COVID-19. The study has identified and prioritized potentially functional gene mutations and provided useful knowledge on genetic regions to be further studied for COVID-19 disease severity. This provides evidence that research on the association between viral genetic variations and disease severity is important [29].

knowledge might be useful for the design and development of COVID-19 treatment and vaccine strategies in the future, to prevent the occurrence of a more severe disease by COVID-19 with further viral genetic changes or a similar scenario caused by second-generation variations.A different study has compared the virulence of SARS-CoV strains with different numbers of spike glycoprotein gene deletion using a reverse genetics approach. The in vitro and in vivo study has shown that the strain without deletion has a higher ability to replicate in the respiratory system and cause extensive lung damage, which is similar to the pattern of severe disease caused by SARS-CoV. These studies have shown that even a small change in the viral genome might greatly affect disease severity [30]. During the SARS-CoV pandemic in 2002-2003, two viral strains with different genetic changes at 29nt were isolated. The strain with deletion at 29nt that had higher affinity for in vitro replication also induced significantly higher production of IL-6 (Interleukin 6) in infected cells and host inflammation compared to the strain without the deletion [30]. An experimental infection of macaque has also shown that the former strain caused higher fever and more severe pathological changes to the respiratory system [31]. This in vivo study might be replicated by a mice model to further prove the association between this genetic variation and the increased disease severity. The knowledge from the study might be useful for the development of intervention strategies to prevent a similar scenario caused by SARS-CoV genetic changes in disease severity to a more severe disease by the current SARS-CoV-2 [31]. . In viral evolution, the genetic mutations might cause changes to viral phenotypes, including disease severity [32]. Genome-wide association studies have successfully identified multiple loci in human genetic variants that affect disease severity. However, the impact of viral genetic variants on disease severity is less characterized. A study on viral genetic determinants for disease severity is generally difficult due to the confounding effects from differences in host genetic background and environmental factors [32].

4. Third Generation Variations

Identification and Characterization of Third Generation Variants The third generation of the SARS-CoV-2 virus began with the identification of the D614G substitution, which has now become the globally dominant form of the virus [32]. A recent study has demonstrated that the G form is more infectious than the original D form. There have been reports of an increase in viral load in COVID-19 patients in association with the G form, though there does not appear to be a difference in disease severity These reports of increased infectivity have led to the discontinuation of certain contact tracing efforts in association with the G form, as it has become too prevalent to effectively continue tracing all cases [33]. The same study identified a strain lacking the D614G mutation, and constructed pseudotyped viruses with D to G mutations at the 614 site of the spike protein, showing that the G form leads to increased infectivity and transmission [33]. In addition to the D614G substitution, Japan has recently identified a distinct strain of the virus with a 12bp deletion in the ORF6 gene, which has now become the predominant form of the virus in that country (Miorin L et al 2022). The third-generation variations in Severe Acute Respiratory Syndrome-related Coronavirus 2 (SARS-CoV-2) have been identified in East Asia, Europe, and North America. Of the 27 mutations identified, the D614G substitution

has become the globally dominant form [33]. The increase in prevalence of the G form has been associated with a significant increase in the rate of spread, and has replaced the ancestral SARS-CoV-2 virus, although there does not appear to be a difference in the severity of the disease associated with the different forms [31]. Given that this mutation was originally identified in the second generation strains and has since become dominant, it has been argued that the third generation of virus should be classified as beginning at the time of the D614G mutation, as this would significantly impact vaccine strategies [32]. Unfortunately, there has been no published work on third generation vaccines, as first and second-generation vaccines are still in the process of testing and validation [33].

4.1. Identification and Characterization of Third Generation Variants

Detailed analysis of the B.1.617 lineage highlights a collection of mutations that characterise it as an emerging VOI. Utilising a PANGO lineage nomenclature methodology (a dynamic nomenclature that utilises regular linguistic characters to identify global circulating lineages of SARS CoV-2), B.1.617 has been classified into three sub-lineages termed B.1.617.1, B.1.617.2 and B.1.617.3. Due to potential public health significance, these sub-lineages have been named as individual third generation variants, each with the defining feature of shared mutations alongside unique mutations [34]. The introduction of the vaccine for COVID-19 was a monumental achievement in the fight against the pandemic. However, the survival of the virus was also a formidable opponent, evolving in response to the immunity provided by the vaccine. This resulted in new variants of the virus, some with unfortunate increased infectiousness and disease severity [34]. These "second generation" variants are defined by having made adaptive mutations enabling increased viral fitness in a background of circulating first generation SARS- CoV-2. However, in the time frame of January to June 2021, a review of communication reports and pre-prints conducted by the COVID-19 Genomics UK (COG-UK) consortium noted that a pattern was emerging of a very large number of spike mutations occurring concurrently across the world, suggesting stepwise adaptive evolution. This series of mutations lacked common mutations seen in the VOCs of the time, primarily occurring in an emerging lineage termed B.1.617 [35].

4.2. Global Distribution and Spread of Third Generation Variations

Third generation variations of COVID-19 have been observed to be the dominant clusters of viruses going through circulation [35]. Having originated in Europe, such new generation variants have been identified in various countries across the world, suggesting the global distribution and spread of these genetic changes. The first third-generation variant to be identified was from a virus sample collected in the UK, between September and December 2020. This variant was identified by an unusually large number of mutations in the spike protein. The increased number of spike mutations have been observed to define several different clusters of the COVID-19 virus. The UK identified variant has since spread to at least 31 other countries/regions [36]. Another distinct third generation variant has been identified in the UK labelled a VUI due to a specific spike protein mutation. This variant came to prominence in December 2020 and was later identified in an increasing number of areas across England and Scotland [36].

A third-generation variant has been identified through virus samples from Denmark. This cluster of viruses has a unique mutation in the spike protein and was associated with an increase in the number of cases in mink in the country. This variant was identified in 12 human cases with 6 different mutations, between September 2020 and January 2021. Most of these cases were related to the mink industry and only 1 case was identified to have spread in the local community. This suggests that although the variant was not widespread, the unique mutation in the spike protein was specific to viruses found in mink, indicating an animal to human transmission and potential back to animal spread [36].

4.3. Comparative Analysis of Third Generation Variants with Previous Generations

The found mutation variants on the Spike protein and its relation to the host is likely the main factor of the rapid increase in cases, given the number of changes that affect transmissibility and immune induction (May A et al 2022). Other than that, the third-generation variants have high potential in immune escape and affecting COVID-19 vaccination. The QDebug mutation, which appears in the Indonesia strain and Thailand strain, is a mutation in position 7 of the translated protein in the ORF10 gene from T to G, causing a change of amino acid from serine to alanine. This mutation had a predicted score in binding affinity of MHC class I downregulation, suggesting it has high potential in immune evasion, which might contribute to the rapid increase in the number of COVID-19 cases in Indonesia [35]. Through comparison on the effect of mutation variants on the host, based on the S- D614 mutation, G614 had been reported to increase infectivity in vitro in both pseudovirus and infectious virus experiments when introduced into USA-WA1/2020 and an early Singapore strain. The increased infectivity was not due to increases in virus production efficiency, but rather increased infectivity per virus particle. This data shows that the D614G mutation has the potential to increase disease severity on the host without increasing efficiency in virus production [36]. Other than that, the age of the sample and the location had a significant effect on the duration from the diagnostic sample to the sequencing of third generation variants. A study reported that the duration from the diagnostic sample to sequencing was 10 days longer with a sample

from an individual aged ≥60 than from an individual aged <39, and the duration was 4 days longer with samples collected in metropolitan municipalities than in provincial municipalities. This data shows that the slow evolution of third generation variants may be related to samples coming from individuals with older age and locations in urban areas [37]. Comparative analysis of third generation variants revealed the fact that they have more similarities than differences. Third generation variants have a common mutation D614G with increased intensity in every variant. The third generation variants also showed a mutation rate of 5.70×10−4 substitutions per site per year, which is relatively slower than the previous generation [38].

5. Impact of Genetic Variations on Vaccine Efficacy

The main purpose of vaccine strategies is to prevent infection and disease. Vaccines that are in use and under development for global use against COVID-19 are based on the original Wuhan-Hu-1 strain that is closely related to the sequence SARS-CoV-2 [39]. As genetic mutations accumulate in the SARS-CoV-2 population across the globe, there is concern as to whether these mutations will affect the efficacy of current vaccines (Kumar S, et al 2022). An immunization response has not been tested in persons who have already recovered from COVID-19. Since reinfection appears to be rare until six months after the onset of symptoms, currently it is not recommended to get the vaccine sooner than that. Patients should be advised that the duration of immunity from natural infection is not known and that they should consider vaccination at some point after they have recovered from their acute illness and their symptoms have resolved [39]. An important question is whether a vaccine can provide better immunity than natural infection. If so, then individuals who have not yet been infected may wish to take greater precautions to avoid infection, knowing that an effective vaccine is forthcoming.

5.1. Considerations for Testing and Surveillance Strategies

Though quantitative data on genetic variability of the virus by location is not yet available, it is known that genetic variation will be a strong influence in the effectiveness of public health measures, particularly those aiming to limit spread at borders or through isolation of hotspots . It may be possible to predict the success of such measures by comparing the genetic variation of the virus with the amount of spread that has occurred (Kaine G, et al 2022). If variation preceded spread, then measures would have been effective, but lack of variation would indicate spread at a time when measures were not in place.Similarly, genetic data could be used to evaluate the success of different strategies in different locations, in particular to compare success in Western countries to that of East and Southeast Asia, This use of genetic data to evaluate past events will inform future public health strategy With the global scale of the COVID-19 pandemic and the variability in effect of public health measures, there has been a vast difference in the success of mitigating spread across the world [38].

5.2. Policy Recommendations for Controlling Genetic Variations

The formula of adaptation, adopt, and abandon underpin this process. Public health measures should adapt in response to changes in the pandemic, adopting new strategies informed by research and evidence, and abandoning old practices that are no longer effective [39]. In the current phase of the pandemic in many countries, a relaxing of measures such as social distancing and use of masks is occurring (Parida SP, Bhatia V, 2020).While this is due to decreased case numbers in the community and is a positive step towards economic recovery, precautions should be taken to prevent a resurgence of the COVID-19 [40] .National lockdown measures have been effective in reducing case numbers in several countries and should be considered if case numbers begin to increase. In the event of increased transmission of COVID-19 or new emerging strains with increased severity, measures such as these may need to be enacted before the situation escalates to crisis point, In the context of global health, it is critical to understand that genetic variations occur in the natural evolution of viruses, and consequently, certain concerns and fears regarding the evolution of COVID-19 are unwarranted. A number of mutations have become fixed within the viral population and an undetermined amount of these could potentially have implications for how the virus is transmitted and the resulting effects on public health. Nevertheless, given the concern that adaptation could result in more severe outcomes, it is of paramount importance to continue to monitor the genomic changes in COVID-19 and their implications on public health [40]

6. Future Perspectives and Research Directions

A second area of research will be to compare viral genetic variations with temporal and spatial patterns of human cases, in order to understand the factors shaping virus transmission and evolution. Given the documented human-to-human transmission of SARS-CoV-2, viral genetic variations will contain rich information about the nature and frequency of different transmission events, as well as potential selective pressures in different human environments and population groups. Epidemiological modeling and phylodynamic inference based on genetic data can be used to generate and test

specific hypotheses about these factors, with direct implications for the design and targeting of public health interventions. This line of research can help to clarify and predict the transmission patterns of new virus strains in both individual countries and for international spread. The first key task is to establish ongoing surveillance infrastructure to monitor viral genetic variations in human populations. These efforts should involve close coordination with public health authorities and international research communities to compare viral isolates and sequences from specific times and locations. While complete viral genomes provide the most precision, targeted analysis of specific variable genome regions across large numbers of cases could yield important surveillance data at reduced time and cost. The current GISAID data sharing initiative is an excellent start, but there is considerable room for expansion and investment in SARS-CoV-2 genomic epidemiology [40].

6.1. Predicting and Monitoring Genetic Variations

The chronicle in surveillance and prophecy of genetic badness and phenotypic name for different generations of SARS-CoV-2 is a complicated one, being heretical- modification-prone and arithmetic-biased. Several inherently detrimental first- generation features have been identified, such as the replacement of the deletions that cause disruption of ORFs and the interference with the host exoribonuclease response at the oligo-uridylate, Ideally, genetic alterations can be monitored using a battery of in silico, in vitro, and in vivo approaches, conducting both targeted specific studies and high throughput direct analyses. In silico techniques involve the use of computer simulations and predictions, which are reliant on the gathering of a comprehensive database of sequence information on SARS-CoV-2 and speculative construction of future virus- host interactions. Fast-forward molecular epidemiology is an approach utilized for real-time tracking of viral spread and evolutionary dynamics, while molecular evolutionary studies using comparative sequence analyses to build evolutionary trees can be used to put genetic changes into an evolutionary framework and evaluate their implications on host-pathogen interaction and disease outcome [41]. The mutation and variants are narrow, due to rate-limiting steps in a bottleneck mechanism such as emergence of a SARS high frequency acuity of a single synonymous mutation in the COVID-19 era, to which it has facilitated a spread back to humans from an animal reservoir (Devaux CA, et al 2022). An efficient strategy to monitor genetic variation is critically underpinned by the need for continued recognition of international collegial resources and information sharing, using an integrated cross-disciplinary approach to improve our understanding of COVID-19 pathogenesis and accelerate further progression .

6.2. Understanding the Evolutionary Dynamics of COVID-19

The ability to effectively predict and monitor changes in the genetic makeup of the virus will greatly enhance our capacity to discern between imported (foreign) strains of disease and those which have emerged locally .This is extremely important given that strategies of isolation and eradication are only relevant to the extent that the disease is not re-introduced from an external source. An imported strain which has become established as endemic in a particular region of the world may be quite different from the original strain of the disease as a result of genetic drift and selection in response to different environmental and cultural pressures, This may affect the efficacy of vaccines and drug treatments developed in response to the original strain. Understanding the global movement and changing genetic makeup of COVID-19 will require the establishment of a comprehensive system of genome sequencing and data sharing between laboratories around the world in a way which is currently not achieved for any human infectious disease (Jones CD, et al 2022).This presents a considerable logistical challenge, but it is achievable given the coordinated global effort that has been successfully mobilized in response to other recent pandemics and emerging infectious diseases. Epidemiological modelling and economic studies indicate that the COVID-19 pandemic is likely to persist for a number of years, possibly cycling through a seasonal epidemic and returning in waves of outbreaks. We hope that as the understanding and technologies developed through this work are applied over the coming years, it will be possible to monitor and react to changes in the genetic makeup of the virus in ways that minimize the global burden of disease [42]. As a highly dynamic RNA virus subject to strong selective pressures from host immune responses and a myriad of environmental conditions, COVID-19 has the potential to evolve rapidly and unpredictably. The possibility of recombination events with other coronaviruses is an additional source of genetic change which could increase the infectivity or alter the disease manifestations for better or worse, Collectively we must remain vigilant and adaptable in efforts to track and understand the genetic evolution of this virus and be prepared to alter public health strategies accordingly.

6.3. Advancements in Genomic Sequencing Technologies

The advancement of genetic sequencing technologies would mark an era of new beginning in the study of genetic variations. Genetic sequencing technologies such as Sanger sequencing and next-generation sequencing (NGS) have been the cornerstone for understanding the genetic variations in viruses. Sanger sequencing, though being a bit slow and expensive, is highly accurate. The accuracy is what makes researchers still choose Sanger sequencing over NGS despite the enormous difference in costs and time. But with the funding from various organizations such as the U.S.

National Institutes of Health (NIH), the Wellcome Trust, and other organizations in many different countries, the production of NGS machines is increasing to aid researchers and public health care to track and monitor the spread of diseases [43]. Next-generation sequencing is highly informative as it allows simultaneous sequencing of a mixed pool of DNA/RNA. This is very useful to track the mutations in the virus as we can compare the sequences with the differing variations in symptoms and severity of COVID-19 cases and draw useful conclusions [44].An article from Science magazine by Jon Cohen and Kai Kupferschmidt exemplifies this, where they were using the NGS machines to sequence and track the mutations of the Ebola virus during the outbreak in Africa to guide the public health officials to where to allocate their resources. This contributed to the eventual disbanding of the outbreak in 2014-2016. With the mutation rates of RNA viruses like COVID-19 being faster than DNA viruses, it is important to develop and further enhance the current sequencing technologies to keep up with the virus [45-51].

7. Conclusion

Finally, the genetic differences in several COVID-19 generations highlight the dynamic character of viral evolution and the necessity of a proactive public health and vaccination development approach. Overcoming the difficulties presented by these variations will mostly depend on constant awareness and flexibility.

Compliance with ethical standards

Disclosure of conflict of interest

None of the author has declared a conflict of interest with respect to this work.

Authors' Contributions

Maha and her team works conceived the idea and wrote the original draft of the manuscript, and the author reviewed and edited the final version.

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