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Mutations: Its Impact on Diagnosis and Development of Vaccines

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ABSTRACT

The Coronaviridae family contains a significant number of lineages seen in a variety of mammals and birds. The propensity of Betacoronaviridiae to switch hosts often suggests that 'SARS CoV-2' is clearly a zoonotic virus. 'SARS COV-2' is an enclosed positive stranded RNA virus that belongs to Nidovirales group. The amount, size, and the type of structural proteins varied significantly amongst Nidovirus groups. In case of COVID-19 virus mutations can be beneficial or deleterious. These can be addition, deletion, inversion. When a virus circulates unchecked and immunisation rates are low or if one dose of a two dose vaccine are given then probability of mutation increases. Mutation rate depends on virus but is affected by natural selection, genetic drift, and other processes like recombination. Various sorts of trials have been undertaken thus far in order to produce an antiviral medication for COVID-19. However some monoclonal antibodies like bevlizumab have been recently approved for COVID-19 infections. The viral genome is sensitive to antigenic shift and antigenic drift while propagating across heterogeneous populace in a variety of conditions. This could lead to the establishment of a resistant strain in the future. Thus causing difficulty in diagnosis and development of vaccines. Various sorts of trials have been undertaken thus far in order to produce an antiviral medication for COVID-19, however none have been successful. Recently there have been much development in field of vaccine development by various companies likes Zydus Cadilla, Pfizer etc. which have showed promising results in providing immunity to common individual against various strains but with on-going and fast mutations changes only time will tell the efficacy of these vaccines against new strains.

Key words: SARSCOV-2, Vaccines, Mutation, Bevlizumab, COVID-19, Nidovirus

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INTRODUCTION

Initially when first case was reported in china it was identified as novel beta coranavirus strain of Coronaviradae family [1]. The Coronaviridae family contains a significant number of lineages seen in a variety of mammals and birds [2]. The propensity of beta coronaviridiae to switch hosts often suggests that 'SARS CoV-2' is clearly a zoonotic virus.

As per various researches, the closest similarity was found to be between the two COVID-19 genomes (99%) compared with that of two bats. Seven complete genomes have been sequenced for variety of 'SARS-COV-2' virus strains and till now they there had been incidences where various strains have been identified like B.1.1.7 in UK and South African variant B.1.351 which shares one mutation with B.1.1.7 [3-5]. In the month of January 2020 or the beginning of February 2020, a "D614G" mutation was discovered in the gene which encoded for the spike protein. With time, the 'SARS-COV-2' mutation was replaced by "D614G" mutation and by June 2020, the "D614G" mutation became the dominant mutation form of the virus circulating round the globe, with enhanced transmission but not severity. Viruses tend to mutate due to some degree of drift which causes change in them. These are a cause of concern because they have made virus more infectious as we have seen in Europe and UK. Recently there have been research articles on finding of a new strain in Malaysia on the 7th and 14th of October 2020, a novel "B.1.524 (G)" lineage with the "S-D614G" mutation was found. This new lineage is not linked to previously known lineages. Among the genetic variations discovered in the novel "B.1.524" was unique 'G114T' mutation in the 5'UTR (G) and 'A701V' in the Spike protein [6].

Over the course of the Coronavirus pandemic, mutations in the coronavirus resulted in genetic heterogeneity in viral strains. Mutations have a significant impact on a number of tests based on different designs, such as molecular, antigen, and serology testing. And hence decreasing their diagnostic efficiency which ultimately leads to requirement for new tests to detect new strains [7].

There has been a major development in production of vaccines across the globe in the past few months since the outbreak of Coronavirus in China around 2020 December. This pandemic has seen development of various nucleic acid based vaccines rather than old conventional ones while various antiviral drugs and other regimes for treating COVID-19 are still being used on trial basis.

LITERATURE REVIEW

This review article focuses on mutations causing variety of strains in different parts of world and associated difficulties in diagnosing a case and what all has been achieved by scientists in the field of vaccines development for the same.

Mutation in COVID-19

SARS-COV-2' is an enclosed positive stranded RNA viruses that belong to Nidovirales group. The amount, size, and the type of structural proteins varied significantly amongst Nidovirus groups. These changes have a substantial impact on the structure and morphology of nucleocapsids and virions [8]. Coronaviridae have the remarkable ability to proofread due all thanks to the nsp14 exonuclease which is a non-structural protein, it excises erroneous nucleotides introduced by their main RNA polymerase nsp12 during nucleotide replication [9,10]. Spike glycoprotein is a host cell entry mediator present on the surface of the virus [11]. The 'SARS CoV-2' surface glycoprotein has 22 N-glycosylation spots for alignment, as well as several additional N-glycosylation sites on the 'SARS CoV-2' spike glycoprotein. This suggests that the coronavirus virus can use various glycosylation to interact with its receptors, which could explain host immunity differences [12].

In case of COVID-19 virus mutations can be beneficial or deleterious. These can be addition, deletion, inversion. These could result in no change at all or they could result in a change in a so a synonymous change is when nucleotide changes but amino acid doesn't change and in non-synonymous mutations amino acid changes can be found.

Mutation rate depends on virus but is affected by natural selection, genetic drift, and other processes like recombination.

Amongst mutations most are found to be deleterious, hence, are removed from the populace by the process of selection. While the advantageous mutation tend to remain in the population by selection. There can also be mutations in which RNA viruses combine with each other and that leads to a greater genetic diversity.

Mutations occur as a result of replication errors, nucleotide damage, or genetic material editing by proteins encoded by the host or specialised structures known as diversity giving rise to retro elements.

The expression of host error prone polymerases may also play a role in viral mutation. Recombination can also help some viruses develop new mutations by boosting the number of copies of their genes or causing genomic rearrangements.

These findings might help with: i) vaccine design markers, ii) novel treatment approaches, and iii) mutagenesis research to stop COVID-19 cells from entering cells. Negative selection in Coronavirus protein coding genes may aid in the characterization of highly conserved areas that can be used to develop novel diagnostic methods in the future.

Mutations: impact on detection of viruses and diagnosis

Due to mutation in initial strain there can be changes in genome sequencing of variants differentiating it from original viral strain already circulating in population. There had been various tests developed for detection of COVID-19 since its outbreak but capability and efficiency of tests may be hampered due to various factors like change in sequencing of strain, design of test etc. The current tests available for detection may be at par in diagnosing strain but a false negative test should not rule out possibility of COVID-19 as the viral strains are mutating at a rapid rate and may give false results.

There are four mutation patterns in the spike glycoprotein of 'SARS-CoV-2' variants of concern: HR-1 ("Heptad Repeat-1"), HR-2 ("Heptad Repeat-2"), "TM" (Trans membrane anchor), "IC" (intracellular tail), "NTD" (N-terminal domain), "RBD" (receptor binding domain), "FP" (fusion peptide) [11]. Like in case of any antigen or serology based test change/mutation in viral spike protein may hamper its performance. Most PCR tests have more than one target and a mutation in one target may lead to 'target failure'. This was seen in the UK with S gene target failure. Regarding whether mutations can cause more severe disease or not public health England reported a cohort study on 1769 controls with similar age, similar gender, similar ethnicity and found that there were no differences in hospitalisations, no difference in death, no difference in re-infections. Secondary attack rates were found to be 15.1% for variant and 9.8% of non-variant [12].

When a virus circulates unchecked and immunisation rates are low or if one dose of a two dose vaccine are given then probability of mutation increases.

The application of molecular surveillance technology is required by new pandemic variants. For identifying 'SARS-CoV-2' variations, the "ADS Spike method" which includes VOC/VOIs, is a cost-friendly, expansible, and efficient solution. The experimental design for SNP calling has also been tested with the relevant controls and parameter modifications. The use of primer mixes to amplify the S gene might speed up the process of finding SNPs, which is critical in a pandemic.

Impact on molecular tests due to mutation

Some of molecular test as approved by the EUA are as follows

Accula Test for SARS CoV-2: By Mesa Biotech Inc.

The FDA's Opinion: When a coronavirus patient has a viral mutation at locations 28881-28883, diagnostic efficiency may be harmed (GGG to AAC). Potential Influence: While it does not appear to have a big impact.

SARS CoV-2 assay kit by linea: By Applied DNA Sciences, Inc.

The FDA's opinion: Due to specific mutations, one of the test's two targets has a drastically reduced sensitivity. Its sensitivity was shown to be considerably diminished due to mutations in the B.1.1.7 variation, affecting its diagnosis.

COVID-19 xpert xpress, COVID-19 xpert xpress DoD, COVID-19 xpert Omni

The FDA's take: While, in most of the COVID-19 molecular tests a single point mutation in target area is unlikely to affect test performance, the FDA's investigation reveals that the Cepheid tests are affected even by a sole point mutation in the target zone of the trial. According to studies, the sensitivity of the test to detect the N_2 target is reduced by two different single point mutations. When enough viruses is present, the E target is yet detected, resulting in a "presumed positive" results in the xpert xpress severe acute respiratory syndrome coronavirus-2 and xpert xpress severe acute respiratory syndrome coronavirus-2 DoD tests.

The xpert omni severe acute respiratory syndrome coronavirus-2 will show "positive" if the E target is detected but the N_2 target is not.

Impact potential: Because the test is designed to discover a variety of genetic targets and these mutations do not cause false negative results, their influence on the test presentation does not appear to be significant (rather noting as "presumptive positive" or "positive" established on identification of the stablished E gene target). In contrast, the FDA is disclosing this information out of an abundance of caution. According to the FDA's investigation, the impact of every one point mutation on test performance is connected to the Cepheid tests' unique chemistry [13].

Taqpath SARS COV 2 combo kit: One of the test's three t argets, counting one of the mutations in the UK variant, has drastically decreased sensitivity because of specific mutations.
The total test sensitivity should not be compromised as t his test is planned to identify several genetic targets. The pattern of identification when particular mutations are p resent could aid in the early detection of new variants in patients, prevent ing infection from spreading further. As is widely known, COVID-19 is a RNA virus with a rapid mutation cycle and great diversity of strains which complicates the development of antiviral antibodies and the achievement of therapeutic change after long investigations [14].

DISCUSSION

Types of vaccines and impact on their development

In theory, extensive genetic data for SARS-CoV-1 should be useful in guiding therapeutic and vaccine development, especially when combined with knowledge of the human proteome and immunological interactions [14].

The S protein's importance in viral entrance creates a good target for coronavirus vaccines. The profusion-state of the Receptor Binding Domain (RBD) is necessary for binding to ACE2, whereas the cleavage site required for viral and cellular membrane fusion is found in the S2 subunit [15].

Various sorts of trials have been undertaken thus far in order to produce an antiviral medication for COVID-19, however none have been successful.

Experimentally it is also shown that non-segmented RNA virus evolves to escape a polyclonal immune response rendering a vaccine ineffective.

N501Y is one of six critical contact residues within the Receptor Binding Domain (RBD) that has been linked to increased binding affinity to the human ACE2 receptor in the United Kingdom. A spike deletion of 69-70 Del has also been observed in conjunction with other RBD alterations on several occasions. The furin cleavage site is directly near to mutation P681H. SARS-CoV monoclonal and polyclonal antibodies in rats struggled to attach to the S protein of SARS-CoV-2 suggesting that initially proposed SARS-CoV RBD-based vaccines need to be revised [17].

Silico was used to develop and launch antiviral drugs for COVID-19 disease, and the results revealed that protease inhibitors can be quite effective in managing the virus. Another study done on three curcumin derived polyphenols looked at their binding affinity to COVID-19's Major Protease (Mpro), and also their enzyme's binding pocket and critical residues.

In the above study, molecular modelling, auto-dock, and molecular dynamics models were used to investigate the conformational and endurance of COVID-19 binding pocket with diferuloylmethane, demethoxycurcumin, and bisdemethoxycurcumin. These results can be used to work on developing COVID-19 treatments based on curcumin-derived polyphenols.

Other organizations have embraced plasmid-based technologies for electroporation driven DNA delivery in combination to nanoparticles, with the intention of providing coronavirus vaccination *via* spike protein creation [18].

Besides, Zydus Cadila developed ZyCoV-D, a DNA plasmid that executed ably in the preclinical examinations and has proceeded to a phase 3 human vaccination trial, where it is now being used to vaccine people all over the world. We'll know how effective it is against mutations once trial data is published.

Plasmid DNA vaccines, according to a study, do not elicit a strong enough immune response, necessitating multiple injections or the use of an adjuvant to boost adaptive immunity [21].

As a substitute for engaging nanoparticles for coronavirus vaccine production, whole spike protein or viral components could be encapsulated or self-assembled in nanoparticles.

Advances in nanotechnology have facilitated the rapid development of novel candidate vaccination formulations. Latest nanotechnology policies with desired physical, chemical, and biological qualities, like polymer matrixes and hydrogels, or recently developed nanotechnology platforms with desired physical, chemical, and biological qualities, are promising for targeted antigen delivery and disease transmission prevention [19].

Despite the fact that various peptide vaccines were developed and are used in preclinical testing, only a few Coronavirus peptide vaccines managed to enter clinical trials.

“EpiVac Corona” for example, is a Russian-based vaccine that combines synthetic SARS-CoV-2 peptide antigens with a protein carrier and is adsorbed over an aluminium containing adjuvant [20].

After intramuscular delivery, this vaccine has proved to truly produce/create protective immunity in phase 1 and 2 clinical studies. Another example is “UB-612”, a peptide vaccine that has progressed through phase 2 and 3 clinical trials and was developed by COVAXX and united biomedical [21].

Because vaccination effectiveness has floated as mutations in concern variants have been acquired, Coronavirus might have a similar phenotype to "influenza mismatch," which is produced by substantial and minor changes in circulating viruses. As a result, the virus in the vaccination did not match the circulating strain, reducing its efficacy. The creation of a quadrivalent inactivated vaccine based on the most frequent strains detected in the previous season under continual observation was prompted by the recurring mutations of influenza viruses. While spreading through diverse populations under a range of settings, the viral genome is susceptible to antigenic shift and antigenic drift. This might eventually lead to the emergence of a resistant strain. A mutation force can be formed by putting too much pressure on the S protein as a target antigen. Vaccination, like in the case of influenza, can help to create seasonal immunity. In addition to vaccine development, vaccine distribution across the world is critical to the achievement of strategic herd immunity through vaccination [22].

CONCLUSION

During a pandemic, monitoring circulating strains is critical for understanding viral strain dynamics and the emergence of new variants.

The goal of this research was to find evolutionary differences in a significant number of severe acute respiratory syndrome coronavirus-2 genomes and speculate on their implications. Positive selection pressure and mutations affecting a specific gene encoding protein (surface glycoprotein) were discovered, which could be utilised to generate vaccines and/or medical medications (nsp12). Negative selection, which has been observed in multiple COVID-19 protein coding genes, could contribute in the development of new diagnostic procedures. Finally, pinpointing specific COVID-19 glycosylation sites may help in understanding the virus's relationship with its receptor and future mutagenesis research, both of which are important for efforts to hinder COVID-19 entrance into cells.

Identifying putative COVID-19 adaptation indicators, on the other hand, is crucial for guiding the production of vaccines and treatment approaches. Thus, Coronavirus mutations must be thoroughly investigated, especially for developing treatments, vaccines, and phenotypic diagnostics.

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