Review Article

Balance and genetic mechanisms in the covid-19 process of mutation.

ABSTRACT

Introduction: SRAS-Cov-2, First found on December 2019 in Wuhan China has turned into a worldwide health care problem. The changes on genetic drift, genetic recombination, natural selection, and other mutations originated variants of medical concern because of the changes on its transmissibility, pathogenesis, or its capacity to avoid the immune system. This is mainly because of the mutations on the structural proteins as the spike protein.

Objective. Describe the COVID-19 mechanisms of mutation.

Methodology. A systematic review was carried out, the search for information was carried out in journals indexed in (Crossref, Google Scholar, SciELO, and in Journals indexed in SCIE, SSCI, ESCI) using keywords; COVID-19 genome, COVID-19 mutations, COVID-19 variants.

Results. The main mutations among COVID-19 variants are due to the Spike protein in its N501Y and D614G forms and modifying the N-terminal domain; likewise, there are mutations in the other structural proteins M, E and N and in the ORF1a and b regions. It has been shown to be multifactorial as it is influenced to mutate by environmental factors.

Conclusions. A detailed comparison was made of the main pathogenic and genetic characteristics of the variants of medical importance in the COVID-19 pandemic. It has been shown to be multifactorial as it is influenced to mutate by environmental factors. For this reason, it is important the correct execution of public health and the application of programs focused on the prevention of contagion and improvement of habits and care to avoid the evolution of the pathogenesis of the virus.

Key words. COVID-19 mutations, COVID-19 variants, COVID-19 genome

INTRODUCTION

SARS-CoV-2, a virus that originated in December 2019 in Wuhan City, China. in the second half of 2019 has spread to 213 nations, regions and territories [1-3]

The pandemic caused by the SARS-Cov-2 coronavirus (COVID-19) has been devastating to health systems worldwide. Since the first cases of the disease reported in December 2019, PAHO has reported 175,701,207 cases of confirmed infections and more than 2.8 million deaths in the Americas region till August 2022[4] and in Mexico it caused about 7.1 million cases and on average 330,000 deaths since it emerged[5]. "Pandemic" is the term WHO (World Health Organization) has applied to the COVID-19 outbreak on March 3, 2020.[6]

Young people usually present mild symptoms, especially if they have a good history of habits, but, the virus can be a precursor to severe respiratory disease mainly in the elderly and those with

comorbidities such as heart disease, diabetes, hypertension, cancer or pre-existing respiratory disease.[1]

The collateral effects of the pandemic onset conditions resulted in the alarming spread and complications of the disease. For this reason, public efforts are focused on combating those variants with a high mortality rate.

Coronaviruses (CoVs) are a group of viruses belonging to the Coronaviridae family. They have an enveloped, single-stranded RNA and a genome of approximately 30,000 bases with 50 cap structures and 30 adenines in the poly-A tail[7]. The characteristic spikes on their envelope resemble a crown structure. SARS-CoV-2 infects cells by interaction of its membrane glycoproteins, especially protein S (spike) with the angiotensin-converting enzyme receptor 2 (ACE-2)[8]. The spike protein is one of the most important structural proteins of SARS-CoV-2 and plays a major role in virus attachment to the receptor followed by its entry into the cell[2].

A mutation tracking system applied to about 200,000 genome isolates yielded about 5,000 mutations in the SARS-Cov-2 spike (S) protein.

Four new variants have rapidly become dominant in their countries, and have raised all kinds of concerns: Alpha (B.1.1.7), beta (B.1.3.51), gamma (P.1), delta (B.1.617.2 and AY lineages) and more recently omicron (B.1.1.529 and BA lineages)4 . These variants are referred to as "Variants of Concern" (VOC) and are the variants that pose a degree of global public health impact. According to the Center for Disease Control and Prevention (CDC), variants classified as VOCs increase their transmissibility, make the course of the disease more severe and reduce the effectiveness of treatments. By far, the omicron variant is the most genetically changed[9].

There is another group of variants called "variants of interest" (VOI). These variants present changes in the virus genome that affect transmissibility, pathogenesis or ability to evade the immune system, but are of less epidemiological importance, although they can mutate and become a variant of concern.

The remarkable observation from this information is that variants born by tiny genomic changes have proven to be exaggeratedly more contagious than their predecessors, plus the healthcare system is faced with a significant increase in hospital admissions every time a subvariant fuels a new wave[10].

Viral mutations may become increasingly common as a result of natural selection, genetic drift, or epidemiological trends. The Omicron variant of SARS-CoV is increasingly reporting cases and contains a unique combination of mutations that could help it spread faster[1]. Although viewed from another perspective, most mutations have minimal or no impact on viral properties. However, some mutations affect the ease of transmission, severity of disease, effect of drugs, effectiveness of vaccines, diagnostic tools, or future community and health measures[11].

In addition to these elements, human genetic factors have great relevance in the mechanism of COVID-19 infection. The inheritance of different degrees of susceptibility to infection is associated with genetic polymorphism in several genes, specifically in those encoding viral entry. These changes are transmissible from generation to generation and are detectable in at least 1% of the population.[12]

The aim of this article is to describe and compare the main mechanisms of regulation and genetic balance of the main COVID-19 variants.

MATERIAL AND METHODS

A systematic review was carried out, the search for information was carried out in journals indexed in (Crossref, Google Scholar, SciELO, and in Journals indexed in SCIE, SSCI, ESCI) using keywords; COVID-19 genome, COVID-19 mutations, COVID-19 variants. This article is of a since it is based merely on the collection, observation and comparison of previously selected sources.

RESULTS

All viruses mutate over time to adapt to changes in the host or environment and COVID-19 is no exception. Most of these mutations have little or even no impact on the properties of the virus. However, when they do generate major changes they are mainly reflected in 3 elements:

- Exaggerated transmission with sudden epidemiological changes
- Increased prevalence
- Low effectiveness of governmental measures against the disease

Thus, there are 2 classifications for SARS-CoV-2 variants according to WHO (World Health Organization): Monitoring (Alpha, Beta, Gamma, Epsilon, Eta, Iota, Kappa, Mu, Zeta) and Alarm (Delta and Omicron) variants[3].

The Delta variant (B.1.617.2) was first described in December 2020 in India, then rapidly spread to many other parts of the world. It has ten mutations (T19R, G142D, 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N) in the S protein[14]. This gives it a greater ability to infect cells and introduce its genetic material into them; it also allows it to better evade the immune system.

The first infection of the Ómicron variant was in November 2021, it has its main mutations in the ORF1a and b regions, as well as in the structural proteins S, E, M and N. It is believed, mainly from phylogenetic studies, that Ómicron arose from the first sequences of SARS-CoV-2 and not from the closest previous variant which is Delta. It has also been proposed that Omicron is the result of COVID-19 infection in immunocompromised individuals such as HIV patients or in non-human hosts that eventually complete a cycle of reinfection. [14]

The mutation rate of this virus is not as high as expected, but it should be noted that it is very well balanced, the mutations that do occur are meticulously selected by these regulatory mechanisms, only those that improve transmissibility or increase the ability to evade the immune system are able to persist.

(*Table 1)* summarizes the main mutations of both variants of interest and of concern and the phenotypic changes they present. Since the beginning of the pandemic in 2020, 3 major waves have been unleashed worldwide; the first one increased daily infections by 50% and was associated with the Beta variant, the second one, associated with Delta which increased daily

infections by 80%, and finally, the 3rd wave associated with Omicron which increased infections by 90%[8]. All this indicates that Omicron is probably the most infective so far.

Table 1. Variants of COVID-19 during the pandemic, their changes and differential phenotypic changes.

Variant	First samples	Lineage	VOC/VOI	Mutations in protein S	Phenotypic changes
Alpha	United Kingdom. December 2020.	B.1.17	VOC (Variant of concern)	D614G, N501Y, P681H.	30-90% higher transmissibility and 50% higher mortality.
Beta	South Africa. December 2020.	B.1.351	VOC (Variant of concern)	D614G, N501Y, E484K	Increased transmissibility and immune system escape. Reduces the efficacy of some available vaccines.
Gamma	Manaus Brazil. December 2020.	P.1	VOC (Variant of concern)	D614G, N501Y, E484K, K417T.	1.4-2-2-2% higher transmissibility, capable of evading up to 60% of protective immunity following previous infection with another variant.
Delta	Prevalent variant in India. October 2020.	B.1.617.2	VOC (Variant of concern)	D614G, P681H, L452R, T478K.	Greater transmissibility, severity and escape from natural and artificial immunity than the alpha variant.
Épsilon	United States March 2020.	B.1.427	VOI (Variant of interest)	D614G, W152C, L452R.	Increased transmissibility, reduced sensitivity to vaccines. 20% more infective.
Zeta	Brazil. April 2020.	P.2	VOI (Variant of interest)	D614G, E484K, V1176F.	Possibly greater escape of the immune system.
Eta	Multiple countries. December 2020.	B.1.526	VOI (Variant of interest)	D614G, E484K, Q677H.	Possibly greater escape of the immune system.
Theta	Philippines. January 2021.	P.3	VOI (Variant of interest)	D614G, E484K, N501Y	More resistant to antibodies and immune response, including the artificial response of vaccines.
Iota	United States. November 2020.	B.1.526	VOI (Variant of interest)	D614G, E484K, S477N.	Possibly greater escape of the immune system.
Kappa	India. October 2020.	B.1.617.1	VOI (Variant of interest)	D614G, E484Q, E154K, V382L, L452R.	Possibly greater escape of the immune system.
Lambda	Peru. December 2020.	C.37	VOI (Variant of interest)	D614G, L452Q, F490S, T859N.	Possibly greater escape of the immune system.

Ómicron	Multiple countries. November 2021.	B.1.1.529	VOC (Variant of concern)	K417N, S477N, A67V, T95I, Y145D, Q493R, L212I	Increased transmissibility, causing outbreaks at a higher rate, resistance and neutralization of antibodies.

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Table 2 highlights the 3 mutations that are most relevant. The most relevant is D614G which seems to make the virus much more invasive against the cell and a more efficient insertion in the immune system and is present in almost all VOC and VOI of public health importance, with the exception of omicron. This mutation originated in January 2020 and by 2021 it was already the predominant mutation in the world, at the moment about 98% of the variants present it.
The omicron variant has some variants in common with other VOCs, but 45 of its mutations are its own, which gives it exotic characteristics of transmissibility and unaffectability, it is 100% more transmissible than delta, it is of rapid expansion and is associated with a reduction in the number of hospitalized patients since the symptomatology it presents is not very aggressive compared to alpha or beta.

Table 2. Mutation and phenotypic changes in COVID-19

Mutation	Genotypic change	Phenotypic change
D614G	Makes cleavage more efficient, promotes virus binding with ECA-2, more efficiently incorporates the virion.	Greater infectivity, it is transmitted and generates copies of its genome faster, it confers greater flexibility and structural stability.
N501Y	Increases affinity for ACE-2. Changes aspargine (N) to tyrosine (Y).	Increased infectivity. Evasion of specific antibodies.
P681H	Adjacent amino acid change allows further viral cleavage and fusion.	Increased infectivity. Evasion of specific antibodies.
L452R	Changing the amino acid from leucine to arginine results in stronger binding to ACE-2	Increased infectivity. Evasion of neutralizing antibodies.
T478K	Change of amino acid threonine to lysine	Increased infectivity. Evasion of neutralizing antibodies.

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Among the newer variants, B.1.640.2 stands out. It does not yet have an official name, however, it has been named IHU after the researchers who discovered it. It is described as containing 46 mutations and 30 deletions resulting in 30 amino acid substitutions and 12 deletions. On the other hand, there are 4 variants with mutations in the same structures: B.1.1.7 (23 mutations with 17 amino acid changes) first described in the UK, B.1.351 (23 mutations with 17 amino acid changes) first described in South Africa, B.1.351 (approximately 35 mutations with 17 amino acid changes) first described in Brazil and B.1.617 first described in India. All of these have mutations in the receptor binding domain of protein S (RBD), of which the N501Y mutation is

common in all, this is to change the amino acid aspargine (N) to tyrosine (Y) at position 501 of the RBD, this simple change causes the virus to bind more easily to the ACE2 receptor giving the virus greater ability to infect[15]. The B.1.351 and P.1 variants have two additional mutations in the receptor binding domain, K417N/T and E484K.

Multiple alignment of all genetic sequences available in GenBank and GISAID for the SARS-CoV-2 protein surface glycoprotein from different isolates showed that there is a rapid occurrence of mutations in the amino acid sequences. The analysis showed that the mutations are scattered in isolates from different regions of the world, with a significant proportion from European states. In total 63 different substitution mutations and 1 deletion were observed. [9]

Mutations were identified mainly in the surface glycoprotein sequence. Mutations were regularly found to cluster around the N-terminal domain (NTD), the receptor binding domain (RBD). The N-terminal domain (NTD) showed 14 substitutions and a single deletion mutation found in 28 different variants.2

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The receptor binding domain (RBD) showed 12 substitution mutations that were identified in 19 different isolates. V367F was found in six isolates originating from France and Hong Kong. In addition, V483A was identified in three isolates from the United States.

Note: Omicron subvariant BQ.1.1 "hellhound".

In recent months it is worth mentioning the emergence of a new subvariant of medical importance which is a new mutation of the omicron variant called BQ.1.1 or colloquially known as "hellhound", it is believed to have originated from repeated infection of populations with low vaccination rates. The main characteristic of the omicron subvariant family is its high risk of reinfection, and it has been shown to surpass the capacity of action of monoclonal antibodies as a treatment alternative. The CDC (Center for Disease Control and Prevention) even foresees a new wave of SARS-Cov 2 caused by BQ.1.1.

Unlike others, this subvariant is mutated in such a way that it increases its capacity for transmission, reinfection and immune evasion due to continuous changes in the receptor binding portion of the protein S receptor, specifically in L452R, F486V and Q493R as they directly modify the interaction with angiotensin-converting enzyme 2 (ACE2).

As a defense against this new threat, the effectiveness of bivalent omicron reinforcements is being investigated, as well as the BA.5 subvariant.

DISCUSSION

The resulting variants of medical relevance are mainly Beta, Delta and Omicron, all of which share the fact of having marked waves of epidemiological relevance throughout the pandemic due

to their high virulence, as well as the qualification of alarm variants. In addition to this, a common factor in these and all variants is the mutation of protein S, mainly in a receptor binding domain (RBD), one of the most remarkable being N501Y, which exchanges bases generating a change of 1 amino acid. Another relevant mutation in this protein is D614G which is present in almost all variants and is key in transmissibility and infectivity. Finally, relevant genetic changes are also shown in the other structural proteins of the virus such as E, M and N, as well as in the ORF1a and b regions.

The impact left by the variants can be seen over time, the mutations adapt to the regulation mechanisms of the virus. In recent years there have been waves of contagion worldwide after starting only in certain countries, perhaps, for each mutation that occurs, the methods we have for epidemiological control become less effective as was the case of Omicron, which despite the fact that most of the population complied with safety measures, the variant spread with an ease never seen before. Fortunately, the genome of the virus favored transmissibility and not pathogenicity, but what if this were not the case, is the world prepared to face new mutations and variants? The appearance of these mutations will continue to occur as long as there is a lack of adherence to public health methods. Moreover, the development of possible more versatile and transmissible variants calls for the creation of vaccines and new public prevention measures because the most important thing is to suppress virus replication at the population level and this can only be achieved through effective public health measures.

SARS-CoV-2 or commonly known as COVID-19 is a novel RNA coronavirus that has caused significant morbidity and mortality worldwide and continues to spread rapidly[1]. Recently, SARS-CoV-2 has been shown to enter epithelial cells through the interaction of its surface glycoprotein with human angiotensin-converting enzyme 2 (ACE2) found on the surface of the epithelium[8]. The mode of entry is through interaction of the receptor binding domain (RBD) of the surface glycoprotein with the aforementioned membrane enzyme of the host cell. Accordingly, 12 substitution mutations in the RBD of the surface glycoprotein were identified in 19 isolates from China, USA and Europe. Antigenic drift is the process by which viruses accumulate multiple mutations in the sequence of proteins that the immune system recognizes as non-self and against which it generates neutralizing antibodies. If sufficient mutations in viral proteins accumulate over time, the immune system can no longer recognize viral antigens, which can lead to a significant epidemic or pandemic[9].

It is known that within the COVID-19 mutation line, some mutations have been relatively irrelevant; there are 15 characteristic mutations represented in the S protein domains. Of the 15 mentioned, 8 of them were detected in the S1 domain and the other 6 in the S2 domain and 1 of them belongs to the peptide signals; the latter is mainly observed in the United States.[14]

In comparison to the first variant seen in Wuhan, China, the Delta and Omicron variants showed 99.2% and 99.82% similarity respectively, demonstrating a greater capacity to infect because the

main differences are found in the receptor binding domain.[14] All these changes are supported by environmental and societal factors such as low vaccination rates, environmental temperature, pollution and air quality.[16]

For this reason, the impact of the variants is seen over time, the mutations adapt to the regulatory mechanisms of the virus. In recent years, there have been waves of contagion worldwide after starting only in certain countries, perhaps, for each mutation that occurs, the methods we have for epidemiological control become less effective, as was the case of Omicron, which despite the fact that most of the population complied with safety measures, the variant spread with an ease never seen before. Fortunately, the genome of the virus favored transmissibility and not pathogenicity, but what if this were not the case, is the world prepared to face new mutations and variants?

The appearance of these mutations will continue to occur as long as there is a lack of adherence to public health methods. Moreover, the development of possible more versatile and transmissible variants calls for the creation of vaccines and new public prevention measures because the most important thing is to suppress virus replication at the population level and this can only be achieved through effective public health measures.

CONCLUSIONS

In the previous review paper, a clear comparison of the main pathogenic and genetic characteristics of the medically important variants of the COVID-19 pandemic was made. This virus has been shown to be multifactorial and multigenetic, being influenced by environmental factors, food and contamination, as well as chronic degenerative diseases.

The causes of genetic variability in COVID-19 are uncertain, but the factors that cause mutation of the viral genome are increasingly better understood, and the scientific community and the general public must improve prevention protocols in the event that a new variant of concern appears. For this reason, it is important the correct execution of public health and the application of programs focused on the prevention of contagion and improvement of habits and care to avoid the evolution of the pathogenesis of the virus.

Note: Omicron subvariant BQ.1.1 "hellhound".

Currently, the new subvariant generates a challenge for public health due to changes in the viral genome that involve an increase in transmissibility with respect to the old omicron B.1.1.529 variant. These were caused by the mutation in the L452R gene which phenotypically resulted in increased infectivity and evasion of the immune response to previous infections or immunizations overcoming monoclonal antibody therapy.

As described above, the low rate of vaccination and preventive measures will continue to result in risky mutations in populations.

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