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Mini review

Variants of the ACE2 Gene: The SARV-CoV2 Receptor in Different Human Populations

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Abstract

In December 2019, a respiratory disease called Coronavirus Disease 2019 (COVID-19) emerged in Wuhan, China. In the following year, it was considered as a pandemic caused by SARS-CoV-2, an RNA virus belonging to the Coronaviridae family. Asymptomatic patients are the main spreaders of the infection as well as obstacles to control the disease that can progress to death. Currently, it is believed that the Angiotensin-Converting Enzyme 2 (ACE2) acts as a receptor for the penetration of SARS-CoV-2 into the human cell. Therefore, this review aims to summarize the variability of the genetic variants of ACE2 with the susceptibility to SARS-CoV-2/COVID-19 in different human populations. In two studies, ACE2 expression in Asians was found to be similar to that of other ethnicities. We observed populations with different variants of ACE2 with single nucleotide polymorphism (dbSNP) that causes inter-individual variability and susceptibility to COVID-19. The dbSNP rs4646116 was found in the Finnish and Latin populations; rs4646127 in Asia, Europe, and the Americas; and rs228566 (c.439+4G>A) was found in South-East Asia (MAF = 0,548%). In Italy, three missense variants of ACE2 (p.(Asn720Asp), p.(Lys26Arg) and p.(Gly211Arg)) interfere with the stabilization of the coronavirus spike protein. Given the studies concerning the genetic variations of ACE2 and SARVS-CoV-2, it is possible to assume the consequences for the pathophysiology of COVID-19, formulate therapies, and develop specific vaccines according to the recognized variants, to reduce the severity and the lethality of the disease in the affected countries.

Keywords: Genetic Variants, ACE2, SARS-CoV-2, Coronavirus, Human Populations

Introduction

In December 2019, a cluster of a new infectious respiratory disease was reported in Wuhan, China.[1] The disease, caused by the novel coronavirus, (Severe Acute Respiratory Syndrome – Coronavirus, or SARS-CoV-2), was soon named COVID-19.[2,3] According to the World Health Organization (WHO), a seafood market in Wuhan was believed to be the epicenter of COVID-19, as the first transmissions involved the seafood market-goers.[4] On March 11, 2020, the WHO declared the outbreak of the virus a pandemic.[5] The pandemic began in China but soon spread all over the world. As of January 22, 2021, there was a total of 98,089,877 COVID-19 cases reported, including 2,100,404 deaths.[6]

Because a large number of coronavirus patients can be asymptomatic, these patients can be a potential source of transmission, and severe cases can evolve to a respiratory distress syndrome, which may lead to death.[2] The overall COVID-19 mortality rate in over 219 countries was 269.5 per 1 million people.[6] The cumulative number of COVID-19 related deaths reported by the WHO on January 17, 2021, was 47% in the Americas, 33% in Europe, 9% in South-East Asia, 6% in the Eastern Mediterranean region, 3% in Africa, and 1% in the Western Pacific region.[7]

The following symptoms are typical of COVID-19 infection: fever, thirst, congestion, cough, fatigue, sore throat, diarrhea, and severe bilateral interstitial pneumonia.[2,8] Age and specific medical comorbidities (e.g. hypertension, diabetes mellitus, and cerebrovascular diseases), have been described as the main determinants for the progression of the disease to severe respiratory distress.[2] In addition to the medical comorbidities, most individuals affected by COVID-19 are predominantly middle-aged and elderly males (Median: 47 years;

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Range: 30-79 years). The infection is less severe in children (0.9-2%), while elderly groups are affected with an increased degree of lethality and severity (8-15%).[9,10]

SARS-CoV-2 is a single-stranded RNA virus with a genome of approximately 30 kb, which belongs to the genus Coronavirus and the large family of viruses Coronaviridae.[11,12] SARS-CoV-2 is similar to others in the family of coronaviruses that comprise ten Open Reading Frames (ORFs). The first ORFs (ORF1a/b) resided in the first two-thirds of the viral RNA, being translated into two large-sized polyproteins pp1a and pp1ab, and are processed into non-structural proteins (nsp1-nsp16).[11,12]

Benetti et al.[13] suggested that the host's genetic mechanisms have an important role to play in the susceptibility to SARS-CoV-2 infection. Recent studies with the spike protein for the identification of the SARS-CoV-2 receptor indicated that angiotensin-converting enzyme 2 (ACE2, OMIM: 300335) is the SARS-CoV-2 receptor,[14-16] and this enzyme cleaves peptides within the renin-angiotensin system.[17] The ACE2 gene is linked to the cell membrane of the tissues of the outer layer of the heart, kidneys, intestines, lungs, and arteries. ACE2 is located at chromosome Xp22.2, and encodes a protein of 805 amino acids in length, belonging to the family of ACE.[18-20] This gene acts as an entry point for various coronaviruses in human cells and plays a protective role in acute lung injury.[18,20] It performs important functions for the heart, kidney, fertility, cancer, and also has a high affinity with SARS-CoV-2 that causes severe acute respiratory syndrome.[18,21,22]

In a recent study, the susceptibility of ACE2 and the TMPRSS gene were investigated in diverse populations.[23] Mainly, ACE2 polymorphisms were detected in association with cardiovascular and pulmonary diseases through angiotensinogen-ACE2 intentions with p. Ag514Gly in African and African-American populations.[23] Li et al.[24] point to slight significant changes in the frequency of minor ACE2 alleles between Asians and Caucasians. However, functional studies, mostly in vitro, to elucidate the magnitude of the differences between the populations affected by COVID-19 are still lacking.[24] Therefore, this review aims to summarize the variability of the genetic variants of ACE2 with the susceptibility to SARS-CoV-2/COVID-19 in different human populations.

Allele Frequencies and Variability in ACE2 Expression Across Different Ethnicities

Recently, Li et al.[24] have detected in gnomAD v2.1, 5,693 mutations (177 missense mutations). Four genetic variants were statistically significant in the comparison of allele frequency between Caucasians and Asians.[24] The K26R variant was observed in the a1 helix of the ACE2 gene, the N638S and I468V were located in the middle of SARS-CoV-2, and N720D in the tail.[24] The virus' Receptor-Binding Domain (RBD) can be found in Protein S (peak glycoprotein), which connects to the ACE2 peptidase domain of humans.[24] Yan et al.[25] claimed that the peptidase domain is found in the a1 helix for RBD recognition.

An Italian study compared the rare variants and the frequency of polymorphisms among Asians and Europeans.[26] No statistically significant evidence that ACE2 is associated with major complications of COVID-19 or with sexual conditions has been reported. However, the genetic variants are modulators of SARS-CoV-2.[26] Further studies are needed for experimental validations with large cohorts in different human populations.[23,24]

Figure 1 shows the sample of ACE2 in eight populations. Li et al.[24] reported that among the observed populations, there was a more statistically significant expression of ACE2 in men of the LWK, GIH, and JPT populations, and in women of the LWK and YRI populations (Figure 1). The authors also report that the clinical relevance for susceptibility or increased severity to COVID-19 is still unclear. The lack of clarification of clinical relevance may be due to the size of the effects that were small in the cohort or due to the specific expression of the site (e.g. peripheral blood, alveoli, renal and cardiac tissues) that brings different results in populations.[24,26] In the literature, men are reported to be more likely to suffer more serious complications of COVID-19 than women.[10] In two studies, it was noted that the expression of ACE2 in Asians was similar to that of other studied races.[24,27]

Expression of ACE2 strongly depends on the tissue and the cell type as well as on the state of several diseases.[23,24,28] Therefore, finding differences in ACE2 expression in different populations seems to be quite difficult. In this sense, we need international collaborations for further studies among ethnic groups of the human populations affected by COVID-19 in the 2020-2021 biennium.

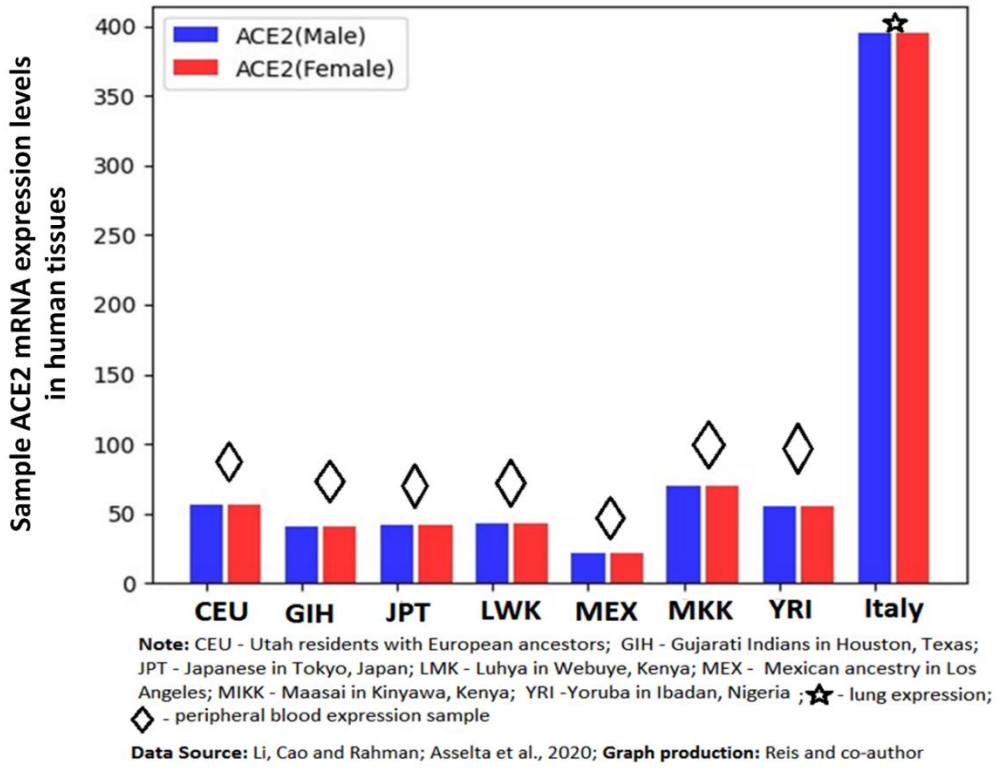

Figure 1. Comparison of ACE2 Expression in a Sample of Asians and others Seven Populations.

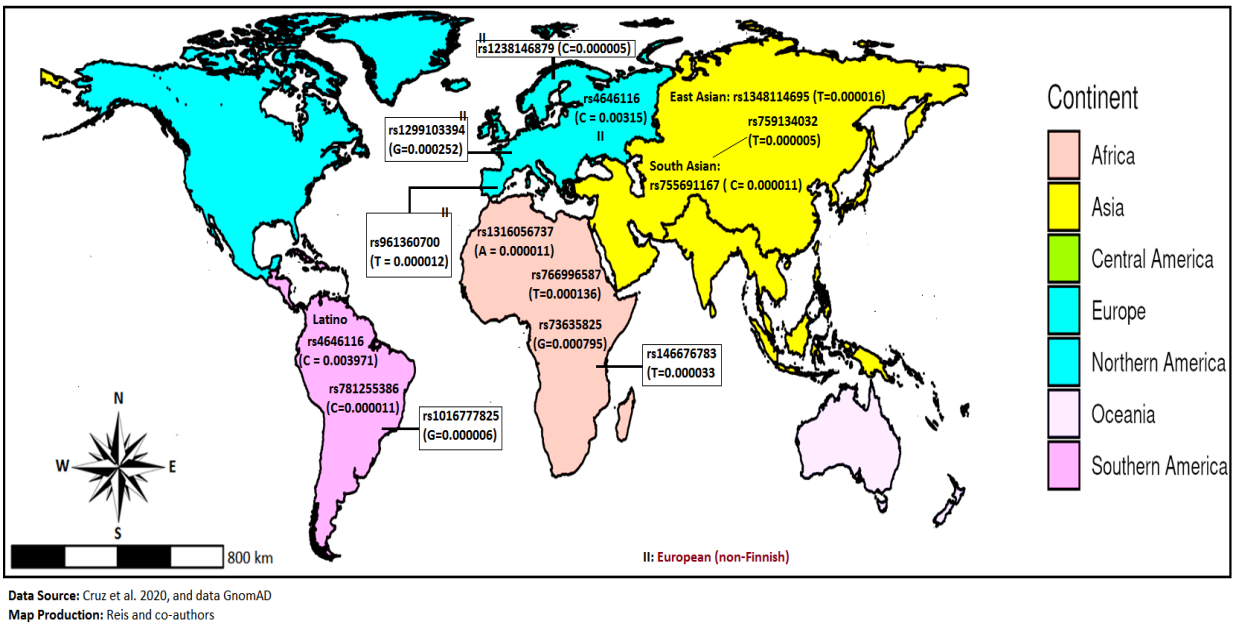

Figure 2. Distribution of Single Nucleotide Polymorphisms (dbSNP) of the ACE2 Gene in Human Populations.

The Single Nucleotide Polymorphism Database (dbSNP) of Human ACE2 from GnomAD Populations

The distribution of 14 dbSNP of ACE2 in populations is observed according to GnomAD data. The dbSNP rs4646116 was the only one detected both in Finland and among the Latino population, and their allele frequency (MAF) was C = 0.00315 and C = 0.00315, respectively (Figure 2), while the frequency in non-Finnish populations were C = 0.003677.[29] Recently, a low MAF in 17 rare ACE2 variants in GnomAD populations has been observed. This can interfere with the analysis of linkage maps that are commonly used for the verification of non-random associations of alleles at different loci.[29] These linkage maps can be used

Table 1. dbSNP Data for the Variants for Human ACE2 Located in Binding Sites with SARS-CoV-2 Spike Protein

Variant	Amino acid change	Chromosomal location	RA	Allele frequency in dbSNP	Population
rs755691167	K68E	chrX:15613110	T/C	C = 0.000011 (ExAC) C = 0.000011 (GnomAD_exome)	South Asian
rs961360700	D355N	chrX:15599350	C/T	T = 0.000012 (GnomAD_exome)	European (non-Finnish)
rs778500138	E35D	chrX:15618929	T/A	A = 0.0003 (TWINSUK)	NA
rs762890235	P389H	chrX:15596342	G/T	T = 0.000024 (TOPMED) T = 0.000034 (ExAC) T = 0.000038(GnomAD)	Latino European (non-Finnish)
rs143936283	E329G	chrX:15599427	T/C	C = 0.000023 (ExAC) C = 0.000028 (GnomAD_exome) C = 0.00004 (TOPMED) C = 0.000091 (GnomAD) C = 0.000189 (GoESP)	European (non-Finnish) Other
rs4646116	K26R	chrX:15618957	T/C	C = 0.002119 (1000Genomes) C = 0.00315 (GnomAD) C = 0.003677 (ExAC) C = 0.003971 (GnomAD_exome) C = 0.004579 (TOPMED) C = 0.005112 (GoESP) C = 0.006203 (TWINSUK) C = 0.009346 (ALSPAC)	Ashkenazi Jewish European (Finnish) European (non-Finnish)Latino South Asian African East Asian Other
rs1316056737	D427Y	chrX:15596229	C/A	A = 0.000011 (GnomAD_exome) A = 0.000024 (TOPMED)	African
rs759134032	P84T	chrX:15613062	G/T	T = 0.000005 (GnomAD_exome) T = 0.000011 (ExAC)	South Asian
rs766996587	M82I	chrX:15613066	C/A,T	T = 0.000011 (ExAC) T = 0.000011 (GnomAD_exome) T = 0.000048 (TOPMED) T = 0.000136 (GnomAD)	African
rs73635825	S19P	chrX:15618979	A/G	G = 0.000795	African
rs1299103394	K26E	chrX:15618958	T/C	G = 0.000252 (GnomAD_exome) G = 0.000345 (ExAC)	European (non-Finnish)
rs781255386	T27A	chrX:15618955	T/C	C = 0.000011 (ExAC) C = 0.000011 (GnomAD_exome)	Latino
rs146676783	E37K	chrX:15618925	C/T	T = 0.000023 (ExAC) T = 0.000033 (GnomAD_exome) T = 0.00004 (TOPMED)	European (Finnish) African
rs1238146879	P426A	chrX:15596232	G/C	C = 0.000005 (GnomAD_exome)	European (non-Finnish)
rs1016777825	R559S	chrX:15589906	C/G	G = 0.000006 (GnomAD_exome)	Latino
rs1348114695	E35K	chrX:15618932	C/T	T = 0.000016 (GnomAD_exome)	East Asian European (non-Finnish)
rs147311723	L731F	chrX:15582265	G/A	G= 0.001996 (ABraOM_exome)	Brazil
rs4646116	L26A	chX:15618958	A/G	A = 0.00110 (GnomAD_exome)	Italy
rs201035388	L8P	chX:15619013	C/T	C = 0.00020	

RA: Reference/Alternative, Extracted and modified from: Benetti et al.[13]; Cruz et al.[29]; database gnomAD (https://gnomad.broadinstitute.org/); ABraOM

to check the correlation between ACE2 dbSNP as a protection item or susceptibility in human populations to COVID-19.[29,30]

Many of the genetic population studies are

concentrated in common variants (MAF≥5%) expected to be found in different populations.[28,29,31] Cao et al.[30] verified that codification variants for ACE2 didn't show any direct genetic evidence that supported the existence of ACE2 variants resistant to the binding of the new coronavirus protein S in different populations. It's important to notice that the study by Cao et al.[30] did not include the variants identified by Hussain et al.[28] Therefore, more studies about the ACE2 gene polymorphisms are still necessary.[29,30] Although several strategies are being developed to evaluate the usage of rare variants in population studies,[32] Cruz et al.[29] affirm that rare variants may not be adequate markers for genetic population studies and demographic differentiation related to COVID-19.

Most of the associations with rare and low-frequency variants demonstrate relatively small effects in complex disease characteristics.[29,31] Although there are resolution limitations, rare variants in association studies are used more and more frequently, and the studies are produced with several alleles of different genes in various populations,[29,31,33] for instance, analytical studies of rare variants facilitate the identification of genes that contain an excess of a rare variation that is probably deleterious among complex diseases traits cases, compared to control cases.[29,32]

Additionally, there is little time of contact between SARS-CoV-2 and humans,[29] which means there is not enough time for a possible selective pressure. On the other hand, not all variants discussed previously and mentioned in this review were described as deleterious, and their effects are unknown. The low MAF for ACE2 rare variants might prevent certain patho-physiological and genetic analysis (Table 1). For example, binding imbalances maps used to analyze the non-random association between alleles at different loci, which could be used to evaluate the correlation between ACE2 variants as a resistance character or susceptibility to COVID-19 in different human populations.[13,29,33] The lack of pathogenicity described to these ACE2 variants (Table 1; Figure 2), with a basis in some predictors, demonstrates that these variants may not offer protection in a level that could elucidate the contrasts in the infection and mortality rates between the world regions affected by the pandemic.[4-6,13,29,34]

Some international studies have identified different variants of ACE2 as causes of susceptibility to COVID-19 in human populations.[35-38] In a population study, dbSNP rs4646127 (log allelic fold change = 0.314%), has been found to have a higher allelic frequency in Asian populations, mainly in China (0.997%), and less frequency in Europe (0.651%) and the Americas (0.754%).[30] In Spain, rs228566 (dbSNP of ACE2) has been associated with elderly individuals with high blood pressure. However, it is statistically less significant among mild or critical COVID-19 patients.[39] In this review, we also noticed rs228566 in Europe and East Asia, with A being the most frequent allele in Italy,[30,40] and the AA genotype giving greater expression of ACE2.[40]

Cao et al.[30] reported that no direct evidence was observed genetically to support the existence of pathogenic variants of ACE2 resistant to the binding of SARV-Cov2 protein S in the studied populations. On the other hand, the authors observed that in East Asia they have higher allele frequencies in the expression quantitative trait loci (eQTL) variants associated with increased expression of ACE2 in tissues.[30] These factors may suggest susceptibility or a differentiated clinical response to SARS-CoV-2 in populations with similar conditions.[30] In contrast to studies already published in the literature, the current studies of COVID-19 should consider combinatorial models, common and rare variants of ACE2 and other genes of interest that partially or fully explain the clinical results of COVID-19.[41]

Studies of the effects of ACE2 at the entrance of SARS-CoV-1 cells showed that the cytoplasmic tail of ACE2 is not necessary for the penetration of SARS-CoV-1.[41,42] However, with SARS-CoV-2, they suggested that the truncated ACE2 could have a therapeutic effect in inhibiting the activity of the SARS-CoV-2 spike protein.[41,43] Computational studies suggest that most ACE2 variants result in similar binding affinity with the SARS-CoV-2 spike protein, and certain ACE2 variants (e.g. rs73635825 and rs143936283) have different interactions with the spike protein.[28,41] Hussain et al.[28] suggested that the rs73635825 and rs143936283 variants positively influence the prognosis of COVID-19 in some people.

Variants with Potential Impact on the Stability of SARS-CoV-2 Protein S

Figure 3 shows 13 variants that are probably pathogenic for ACE2. However, further studies are needed to confirm it. The ACE2 variant with the most allele frequency is c.439+4G>A (intronic variant) in South-

East Asia (MAF = 0.548%). The ACE2 p. V749V variant (MAF = 0.046%) has been observed in ABraOM/Brazil.

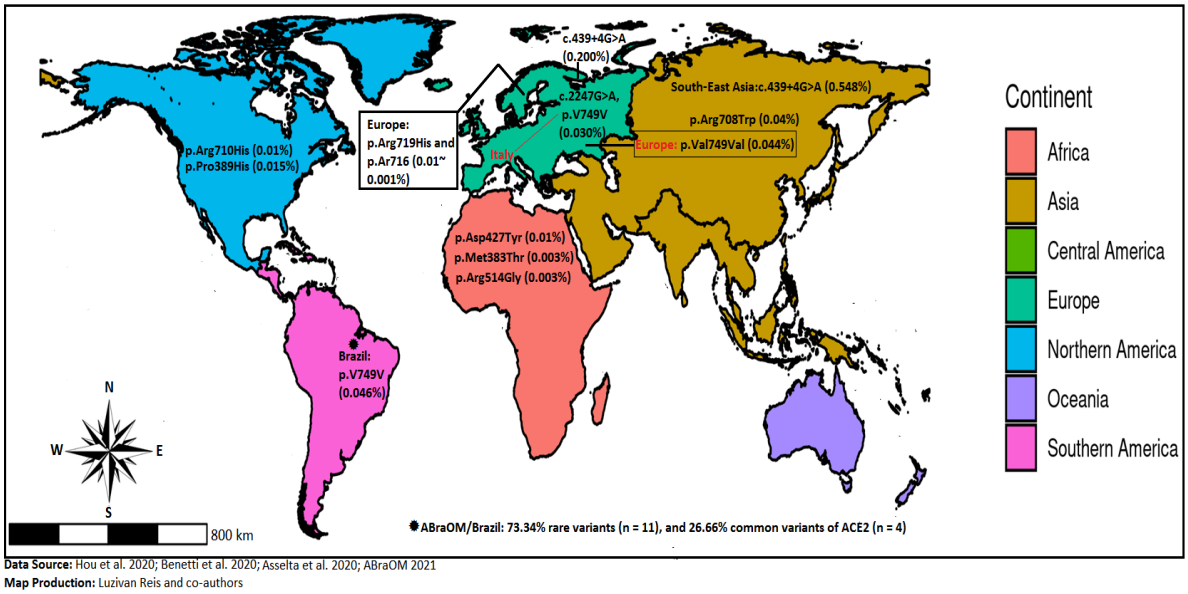

Figure 3. Variants of ACE2 with Potential Impact on the Stability of SARS-CoV-2 Protein.

In that database, 73.34% are rare variants and 26.66% are common (Figure 3). On the other hand, other studies have already described a number of variants with a potential impact on the stability of the SARS-CoV-2 spike protein.[13,23,26] Among these, Benetti et al.,[13] with data from the Italian population, described three missense variants of ACE2 [p.(Asn720Asp), p.(Lys26Arg), and p.(Gly211Arg)] that interfere with the stabilization of the spike protein. The authors also observed two rare variants [p. (Leu351Val), and p. (Pro389His)] that may influence the internalization of SARS-CoV-2 in cells.[13]

In gnomAD (vs 3), Hou et al.[23] found 61 variants of ACE2 potentially harmful in: a) 39% (24/61) in African/ African-American populations, 54% (33/61) in non-Finnish European populations; and b) 2-10% of harmful variants among mixed Latin American, East Asian, Finnish and South Asian populations. In this perspective, the present review highlights the candidate alleles of ACE2 that may bring resistance or greater susceptibility to SARS-CoV-2/COVID-19.[13,40,44] In addition, the review provides a basis for similar investigations regarding the recently reported molecule (TMPRSS2 gene), with TMPRSS2 being necessary to initiate the spike protein for coronavirus cell entry.[44]

The optimization in recognizing the host binding receptor is a crucial step that defines the preference of the virus for a particular tissue or type of cell.[45] Recent studies show that mutations in binding sites of ACE2, e.g. non-synonymous mutations, may alter the conformational structure of the ACE2 protein, hindering the glycoprotein S binding and its stability, thus, making it difficult for the virus to enter.[46,47] SARS-CoV-2 capacity to enter and to infect the cells depends on a few ACE2 factors: a) binding affinity with the SARS-CoV-2 spike; b) amount of ACE2 that migrates from the endoplasmic reticulum to the cellular surface; and c) the ACE2 protein renewal rate in the cell membrane.[46,48] Based on the ACE2 gene function, it could be predicted that hosts of ACE2 negative effects variants minimize the binding affinity with the SARS-CoV-2 spike. For this reason, the susceptibility to SARS-CoV-2 infection would be reduced.[45,46,48] Corroborating, Heinzelman and Romero[46] detected ACE2 variants, p. Ala242Val and p. Tyr252Cys, with a reduced display in the cell surface, so, the ACE2 receptor had binding difficulties with the spike protein. Therefore, it would be expected that the host populations of these two variants had a low probability of showing serious symptoms of COVID-19 in case they were infected by the virus.[46] However, Ozono et al.[48] concluded that the spike mutations (e.g. D614G mutation) increase the host cell entry, having a higher affinity to ACE2—maintaining an increased susceptibility to the infection.

Conclusion

It can be concluded that the clinical manifestations and recovery rates of the disease vary significantly across different age groups, nationalities, and races.[10] Most likely, some individuals who have tested positive for COVID-19 and more or less severe diseases may be due to variants of ACE2 and other genes.[28,41] Therefore, this review provides clues to filter the frequencies of candidate alleles in different populations to predict the prognosis of SARS-CoV-2/COVID-19 during and after the pandemic.[13,28,40,41] In addition, the lack of pathogenicity reported for most ACE2 variants according to various predictors suggests that they may not provide protection at a level that explains differences in infection and mortality rates across countries.[29]

In conclusion, the COVID-19 pandemic is a major challenge for public and clinical health.[14] For clinical management in the near future, we must strive to adopt a customized medical approach to provide individualized treatment to patients affected by COVID-19.[12,14] As highlighted in this review, this should take into account individual patient differences as well as molecular interactions between ACE2 variants with SARS-CoV-2 strains.[14] Mutual interactions of ACE2 with strains of SARS-CoV-2 may occur, for example, with the 501.V2 variant identified in South Africa, the B.1.1.7 in the Netherlands,[49] variant P.1 (mutation E484K) in the state of Amazonas, Brazil, and the VOC 202012/01 identified in the United Kingdom.[35] In this perspective, Novelli et al.[50] speculated that rare susceptibility alleles may be in the non-coding regions of ACE2, known to play a role in regulating the gene.[50] In light of studies on the genetic variants of ACE2 and SARS-CoV-2, the consequences for the pathophysiology of COVID-19,[14] will be made clear. This will allow researchers to support specific vaccine therapies and developments according to the variants observed in order to reduce the severity and lethality of the disease in the affected countries.

Authors' Contributions

Reis LC: has conceived, wrote the manuscript and revised it. Júnior WFS: prepared a table and participated in the revision of the manuscript.

Data availability

Data are available at PubMed, National Center for Biotechnology Information for public consultation, and available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no conflicts interest.

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