Chapter

Co-Evolution between New Coronavirus (SARS-CoV-2) and Genetic Diversity: Insights on Population Susceptibility and Potential Therapeutic Innovations

Mahmood A. Al-Azzawi and Moustafa A. Sakr

Abstract

The DNA sequences are different between the distinct individuals and these variations produce the species genetic diversity. SARS-CoV-2 virus is a zoonotic SARS-like coronavirus that spreads globally, causing the COVID-19 pandemic disease. The immune response genes are the most various and different in the human genome, correlating with infectious diseases. Genetic variants in the angiotensin-converting enzyme 2 (ACE2) receptor, TMPRSS2, HO-1, BCL11A, and CYP2D6 are predicted to either encourage or inhibit the interaction with the viral proteins and subsequently contribute to coronavirus genetic risk factors. The genetic susceptibility to SARS-CoV-2 was investigated by analyzing different genes' polymorphisms such as ACE2 and TMPRSS2, HO-1, and BCL11A. A specific genetic susceptibility to COVID-19 was found through different populations in TMPRSS2, ACE2, HO-1, and BCL11A genes. Particularly, ACE2 gene polymorphisms were shown to be correlated with pulmonary and cardiovascular conditions by modifying the angiotensinogen-ACE2 system, which recommends the possible explanations of COVID-19 susceptibility based on genetic diversity. Moreover, the COVID-19 treatment could be complicated by such genetic polymorphisms. In conclusion, a good characterization of functional polymorphisms and the host genetics can assist in identifying the pathophysiology of the disease pathway to stratify the risk evaluation and to personalize the treatment procedures.

Keywords: gene polymorphisms, infectious diseases, host genetics, SARS-CoV-2, TMPRSS2, HO-1, ACE-2, BCL11A, coronavirus, COVID-19

1. Introduction

Infectious diseases have been and continue to be a source of concern and intimidation for human and animal life, and due to the absence of effective strategies in disease control, epidemics appear and spread day after day and cause a significant increase in mortality. Over decades, genetic and genomic studies provided invulnerable evidence that the host showed a genetic variation in its response to infectious agents, that may otherwise affect epidemiological risks, morbidity, and

survival [1–4]. Determining the host genetic implications in the risk of the epidemic and its severity remains the biggest obstacle to the infectious disease research progression [5, 6]. Because of the large size of the samples required by quantitative genetic studies, the definition of disease resistance based on individual mortality must be changed because it is easy in any case to know if the subjects' mortality was happening due to the exposition to infectious diseases or not. But, this is not true in the case of survival because it is multisided, and it may depend not only on an individual's resistance to infectious agents but also on his ability to survive after getting a disease or infection [7, 8].

Obviously, interest has increased in the infectivity genetic regulation, which can be described as the capability of a pathogen to infect an individual upon contact. Comprehension of the genetic regulation of infectivity is especially relevant if there are contrary genomic associations between these traits and elements of tolerance or resistance [9–11]. Such unfavorable genetic associations could be arising if subjects with much genetic survival not only come over with infection but also have a tendency to shed more pathogens [12]. Endurance and resistance infectivity may be controlled by several gene sets with variable contributions, both in degree and direction for survival [7, 13]. Despite this, no study has investigated these three traits at the same time. It is worth noting that plenty of quantitative genetic studies revealed variation in genetic resistance [2, 14–16], however, only a few studies showed a genetic difference in disease survival [7, 8]. In the context of infectious diseases, genomic selection may definitely restrict the spread of the disease by implementing a mechanism for determining high-risk people of infection [1].

Almost two decades after the outset of the Severe Acute Respiratory Syndrome (SARS), produced by a beta coronavirus, recently called SARS-CoV-1, the world was surprised by the emergence of a more virulent and infectious new virus in late 2019. This virus soon spread to almost all parts of the world and quickly reached the epidemic disease state [17]. The new coronavirus 2019 (COVID-19) outbreak originated from the SARS-CoV-2 virus suddenly became a major public health threat. COVID-19 is characterized by different types of clinical characterizations: affected patients can be asymptomatic, symptomatic with mild respiratory symptoms, or manifest severe pneumonia [18–21]. It is noted that these estimations are variable and began to approach accuracy as more cases are described, examined, and analyzed. Curiously enough, there is a clear difference in these estimations among different countries, worthy to mention that, the differences in the severity of the virus were recorded between the sexes and different age categories [18, 20, 22]. The infected cases have increased drastically [23]. Transmission from one person to another has been confirmed [24]. The virus was discovered in Bronchoalveolar lavage (BAL) [22], saliva and nasopharyngeal swabs [25], sputum [26], and throat [27, 28]. Even though the number of patients with COVID-19 was asymptomatic or mildly symptomatic still indecisive until now, but some studies have suggested that the percentage is between 40 and 80% [29, 30].

Among the most debatable characteristics in the clinical course and pathogenesis of COVID-19 is the heterogeneous hazard in the development to the acute form. Some significant clinical factors have been specified as severe disease predictors in different populations around the world, essentially include old age, male sex, obesity, and presence of multiple co-morbidities, such as diabetes mellitus, hypertension (HTN), cardiovascular disease, and impaired liver and renal function [20, 31–33]. In fact, some patients continue completely without symptoms until the final viral shedding, however, others experience a highly aggressive form of the disease [34–39]. These severe cases in the clinical picture of COVID-19 firmly propose that other co-factors may have a vital role in modifying disease development and progression. The suppressed immune response in the elders, co-morbidities,

or smoking condition, may explain the variances in the COVID-19 disease severity between individuals and populations [40], but severe disease has also been detected in young persons, apparently free from these risk factors. This shows that most risk factors clarifying COVID-19 disease severity are yet mysterious. Therefore, to recognize the mechanisms beyond COVID-19 disease severity is critical to provide suitable protective measures and sufficient triage approaches, drug innovation processes, and eventually the pandemic control. The genetic diversity between hosts can be explained the big difference in the incidence of SARS CoV-2 rates and the severity of COVID 19.

In this chapter, we will focus on some genetic variants and their implications for the severity of COVID-19. From these genes, we will take the consideration of the ACE2, TPRSS2, HO-1, and BCL11A genes, and the association between the DNA polymorphisms of these genes with the genetic susceptibility of the COVID-19, Whereas, systematic investigation of the functional polymorphism in these genes among diverse populations could tile the way for reliable medicine and personalized treatment approaches for COVID-19, this will call genetics to take the initiative in combating the virus pandemic.

2. Pathways of cellular infection by SARS-CoV-2

SARS-CoV-1 and SARS-CoV-2 connect to a similar receptor on the surface of human cells, known as angiotensin-converting enzyme 2 (ACE2) [41]. This complex particularly includes the receptor-binding domain (RBD) positioned within the virus spike protein (S protein). However, recent laboratory studies have revealed that unlike SARS-CoV-1, the SARS-CoV-2 RBD favors creating a greater binding capacity (i.e. 1204 versus 998 Å) [41, 42]. The SARS-CoV-2 infects and enters the infected cell by binding the viral spike protein with ACE2 of the host cell through the RBD. Even so, the splitting of spike protein needs to be done by human protease, where S protein subunits (S1 and S2) are broken apart from each other, with the last domain undergoes considerable structural modifications necessary to bind with the cell membrane of the host cell [43]. The transmembrane serine

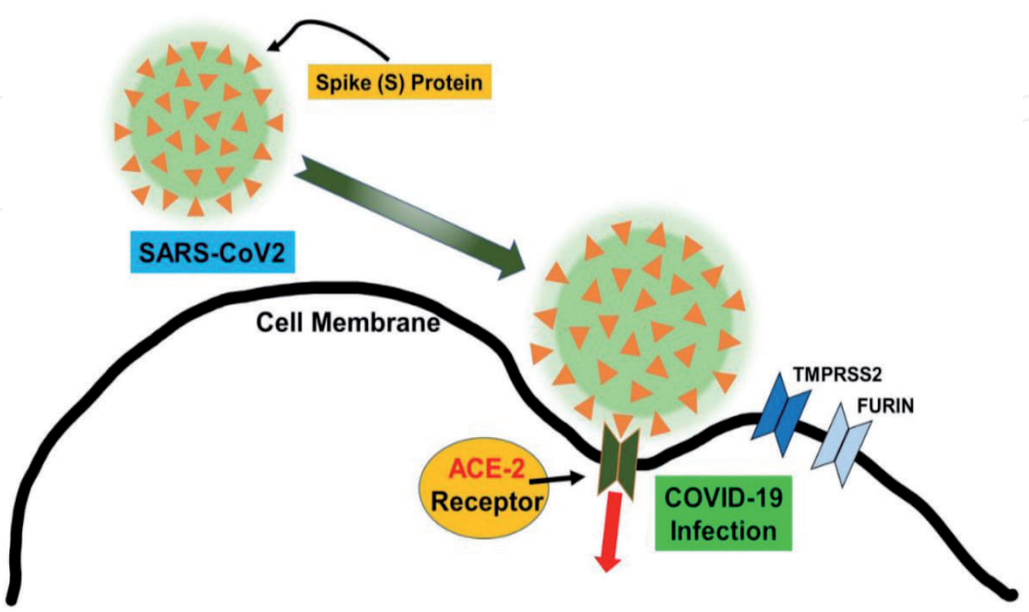

Figure 1.
Illustration of the COVID-19 virus spike protein. Across ACE-2 receptors, the spike invades the cell. Afterward, the spike is cleaved by the host cell proteases, membrane protease 2 (TMPRSS2), and furin, which results in COVID-19 infection activation [48].

protease 2 (TMPRSS2), together with lysosomal cathepsins, considers one of the most crucial proteases in this approach [44]. Moreover, a type 1 membrane-bound enzyme (furin), also splits the site between SARS-CoV-2 spike protein (both S1 and S2 subunits). Most significantly, furin can be expressed in numerous organs, involving the lungs. Furin stimulates the splitting of spike protein (S1/S2) after the binding of SARS-CoV-2 to ACE2 receptor, and this stimulation by itself is necessary to enter the virus into the cell [45]. This different pathway, which includes furin-mediate activation, would allow SARS-CoV-2 to be less dependent on co-expressions of TMPRSS2 on the cell surface of the infect cells. Hence, SARS-CoV-2 could be able to enter a wide range of low TMPRSS2 expressing cells. Lastly, disintegrin and metalloproteinase domain-containing protein 17 (ADAM17) stimulate the release of ectodomains for a number of transmembrane proteins, such as ACE2 [46]. Therefore, increased ADAM17 activity is thought to be correlated with increased shedding of ACE2 and eventually decreases the possibility of cellular entry by SARS-CoV-2 [47] (**Figure 1**).

3. ACE2 expression in human tissues

The expression of ACE2 in the different human tissues was controversial because ACE2 was newly identified as a major binding site across which SARS-CoV-2 enters human host cells. Recently, many studies were performed to detect the cell types where ACE2 receptor is mainly expressed, which could describe the possible SARS-CoV-2 targets. One study was conducted to address the expression of ACE2 in various natural human tissues, and the analysis of the results regarding age and sex. Highest ACE2 expression levels were detected in the tissues of the small intestine, testicle, thyroid heart, adipose tissues, and kidneys. Esophagus, pancreas, lungs, liver, adrenal gland bladder, and colon were found to express the intermediate level while the lowest expression was found in the stomach nerves, blood vessels, uterus, muscle, spleen, bone marrow, and brain. Regarding lungs, the levels of ACE2 expression were upregulated and downregulated in relation to the immune pattern of men and women respectively [49]. ACE2 also was expressed in certain types of epithelial cells in the airway, such as type II alveolar epithelial cells and ciliated nasal epithelium. Moreover, it was found to be highly co-expressed with the TMPRSS2 in the nasal epithelium, which explains their higher infectivity by COVID-19 [50]. ACE2 is localizing also on the oral cavity mucosa. For now, these results revealed the underlying mechanism that the oral cavity poses a significant potential risk for 2019-nCoV susceptibility, and ACE2 was also expressed in lymphocytes inside the oral mucosa [51]. These findings have reminded us that COVID-19 attacks the lymphocytes and causes lymphopenia, mostly in severe forms of the disease [52].

More importantly, ACE2 also are expressed in endothelial cells [53]. That explains why COVID-19 disease affects multiorgan in the patients [54]. these results indicate that SARS-CoV-2 virus promotes the initiation of endotheliitis in many organs as a direct result of the viral intervention and the inflammatory response of the host. Additionally, the triggering of pyroptosis and apoptosis may have an important role in endothelial cell injury in COVID-19 patients and can account for the weakened systemic microcirculatory performance in various blood vessels and their clinical consequences in COVID-19 patients [55]. This supposition affords justifications for treatments to stabilize the endothelium during viral reproduction, especially by anti-inflammatory cytokines drugs, cholesterol-lowering drugs, and ACE inhibitors [56–59]. This approach can be especially appropriate for weak patients with an earlier endothelial disorder, such as hypertension, diabetes mellitus, obesity, cardiovascular disease co-morbidities patients [55].

4. Implication of human polymorphism of ACE2 in disease susceptibility

A lot of ACE2 variants have been recognized in different databases [60, 61]. over the last decades, much focus has been assigned on some of ACE2 polymorphisms, due to their effects on the development of cardiovascular disease (CVD) and, more specifically, their association with hypertension (HT). ACE2 restricts the negative profibrotic and vasoconstrictor influences of AngII, as the breakdown of AngII to Ang (1-7) decreases the AngII oxidative stress of the cerebral arteries endothelium [62]. Ang (1-7) has been stated to have antifibrotic and vasodilation [63, 64]. Low cardiac expression of ACE2 levels has been notified in hypertension and diabetes heart failure [65, 66]. ACE2 gene polymorphisms were first detected in the Chinese people with different ACE2 variants (rs4830542, rs4240157, and rs4646155) linked to hypertension (HT) [67–70]. Also, ACE2 SNP rs21068809 (C > T) was found to be linked to the clinical features of HT [71]. In India, a study of 246 patients with HT and 274 normal subjects showed a connection of ACE2 rs21068809 SNP with HT [72]. in Brazilian cohorts, a study of genetic association of the combination of ACE2 G8790A and ACE I/D polymorphisms reveal susceptibility to HT [73]. ACE polymorphism has been described in African- Americans with HT [74].

5. Viral ACE2 receptor polymorphism and coronavirus infection

ACE2 gene variants are still possible to affect SARS-CoV-2 infectivity. In SARS-CoV, the function of the S1 domain of the S protein is to mediate the binding of ACE2 receptors while the S2 domain is potentially undergoing post binding trans-conformational modulations which activate the fusion to the cell membrane [75]. The viral (RBD) found in S1 has been adjusted to amino acid number 270 to 510 [76]. The Leu584Ala point mutation of ACE2 significantly weakened the shedding activity of the enzyme and promoted the entrance of SARS-CoV into the host cells [77]. An ACE2 soluble form lacks the transmembrane and cytoplasmic domain was stated able to prevent SARS-CoV S protein binding to ACE2 [46]. Recombinant SARS-CoV-2 spike proteins were observed to downregulated ACE2 expression by releasing sACE2 and thus enhancing injury of the lung [78]. SARS-CoV and SARSCoV-2 participate in the identity of 76% of the amino acid residues necessary for binding of ACE2 within the SARS-CoV-2 spike S1 domain. A lot of amino acid residues of the ten human ACE2 proteins were compared by multiple sequence alignment, a 100% identity among the ACE2 sequences was observed in four different ACE2 isoforms. The role of these ACE2 isoforms remains unpredictable in SARS-CoV-2 infection outcome. According to the work by Cao et al., [61] 32 polymorphisms of ACE2, including 7 hotspot variables (Ile486Val, Lys26Arg, Asn638Ser, Asn720Asp, Ser692Pro, Ala627Val, and Leu731Ile/Phe) were identified in different peoples, that make some individuals could be more or less susceptible to the virus than others.

In a preliminary study, the distribution of the allele frequency for 1700 polymorphisms in the ACE2 gene was conducted between various populations of the world. What is noteworthy is that 11 common and rare variants were detected linked to the high ACE2 expression. It was observed that their expression is irregularly distributed among different populations groups. This study found that the polymorphism of the ACE2 gene (variant 4,646,127) was closely related to the higher expression levels of the ACE2 gene in the East Asian population, and this paved the way to study this important issue more specifically [61]. These results were confirmed by a similar subsequent study by [79], which also evidenced that the allele frequency of these variants associated with overexpression of ACE2. Also, different ACE2 polymorphisms encoded a number of proteins for SARS-CoV-2 spike protein has

been studied, and it was found that each variant differs in compatibility with RBD sequence. Specifically, although the majority of genetic variants exhibited high physical similarity. Specifically, the two ACE2 gene alleles (rs143936283 and rs73635825) showed a quite low binding strength for the SARS-CoV-2 spike protein, which could mean a lower possibility of viral binding and possible to infection resistance [80]. It has been observed that the probability of some natural genetic variants of ACE2, particularly those assigned to attach with the SARS-CoV-2 spike protein, may be linked with flexible virus-host interaction, thus likely modifying severity and pathogenicity. A large analysis of the genome data-set was performed and showed that no less than nine human ACE2 variants (E23K, S19P, I21V, N64K, K26R, H378R, T27A, T92I, and Q102P) are prospective to increase predisposition to viral binding, while 17 other variants of ACE2 (that is, E37K, K31R, H34R, N33I, E35K, Y50F, D38V, G326E, N51S, M62V, D355N, K68E, F72V, Y83H, D509Y, G352V, and Q388L) were thought to be protected from viral entry, where they demonstrated a lower binding tendency to SARS-CoV-2 spike protein [81].

In another study, from five separate Italian centers, the authors found that three variants of ACE2 can be specified (p. Gly211Arg, lys26Arg, and p. Asn720Asp). It was noted that these three polymorphisms were recurrently identified in the Italian population rather than the East Asian population. These variants are closely located in the SARS-CoV-2 essential sequence of spike protein binding sites and therefore viral entry and division expected to be modified (for example, Asn720Asp is located on only 4 amino acids of TMPRSS2 cleavage site) [82]. This may tell a partial explanation for the high case mortality rate registered in Italy by comparison to China. Despite ACE2 practically serve as a receptor for coronavirus SARS entry into human host cells, another does not support the correlation between its common gene polymorphisms and receptivity or consequence of SARS [83]. It has also been observed that some ACE2 variants show differential efficacy in stimulating neutrophils, monocytes, natural killer cells (NK), macrophages, and T helper cells, thus

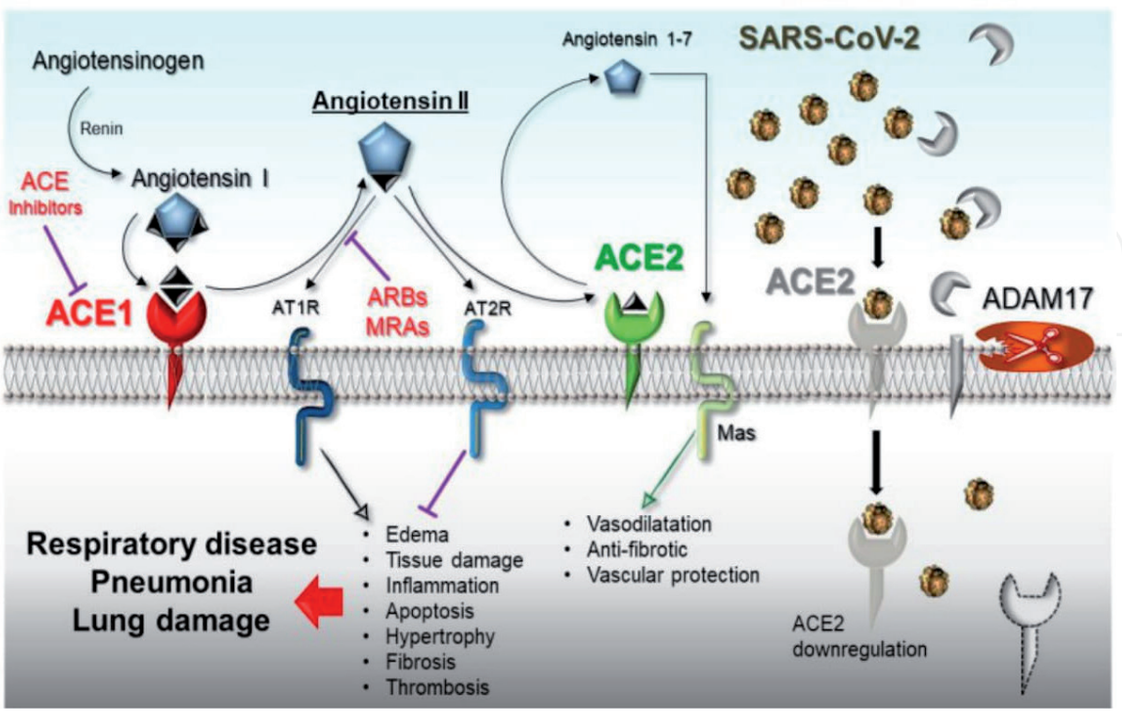

Figure 2.
Diagrammatic representation for the renin-angiotensin system (RAS) pathway. As ACE2/Ang 1-7/ Mas-axis and ACE1/Ang-II/ AT1R-axis occur, SARS-CoV-2 inhibition by cleavage of ACE2 by ADAM17 appears. ***ADAM17:*** *ADAM metallopeptidase domain 17;* ***ARBs:*** *angiotensin receptor blockers;* ***MRAs:*** *mineralocorticoid receptor antagonists [87].*

may probably either enhance or reduce the inflammatory or "cytokine storm" [84], in addition to stimulating the processing of Ang II, thereby improving or exacerbating vasoconstriction and participating to the improvement or exacerbation of topical or systemic tissue infection [85, 86]. (**Figure 2**).

6. TMPRSS2 polymorphism analysis with COVID-19 disease

TMPRSS2 and ACE2 have been associated with SARS-corona (CoV) disease, influenza, and SARS-CoV-2 in facilitating viral entrance into the infected host cell TMPRSS2 considers as an androgen-reactive serine protease enzyme that cleaves SARS-CoV-2 Spike protein, mediating viral activation and entry [88]. Single-nucleotide polymorphisms of TMPRSS2 enzyme have been studied in several diseases such as in breast cancer, the rs2276205 (A > G) with low-frequency allele was correlated with increased patients' endurance [89]. In prostate cancer, the rs12329760 (C > T) of TMPRSS2 has a higher frequency in men with prostate cancer in his family, while ERG gene fusion [90, 91] Rs383510 (T > C) and rs2070788

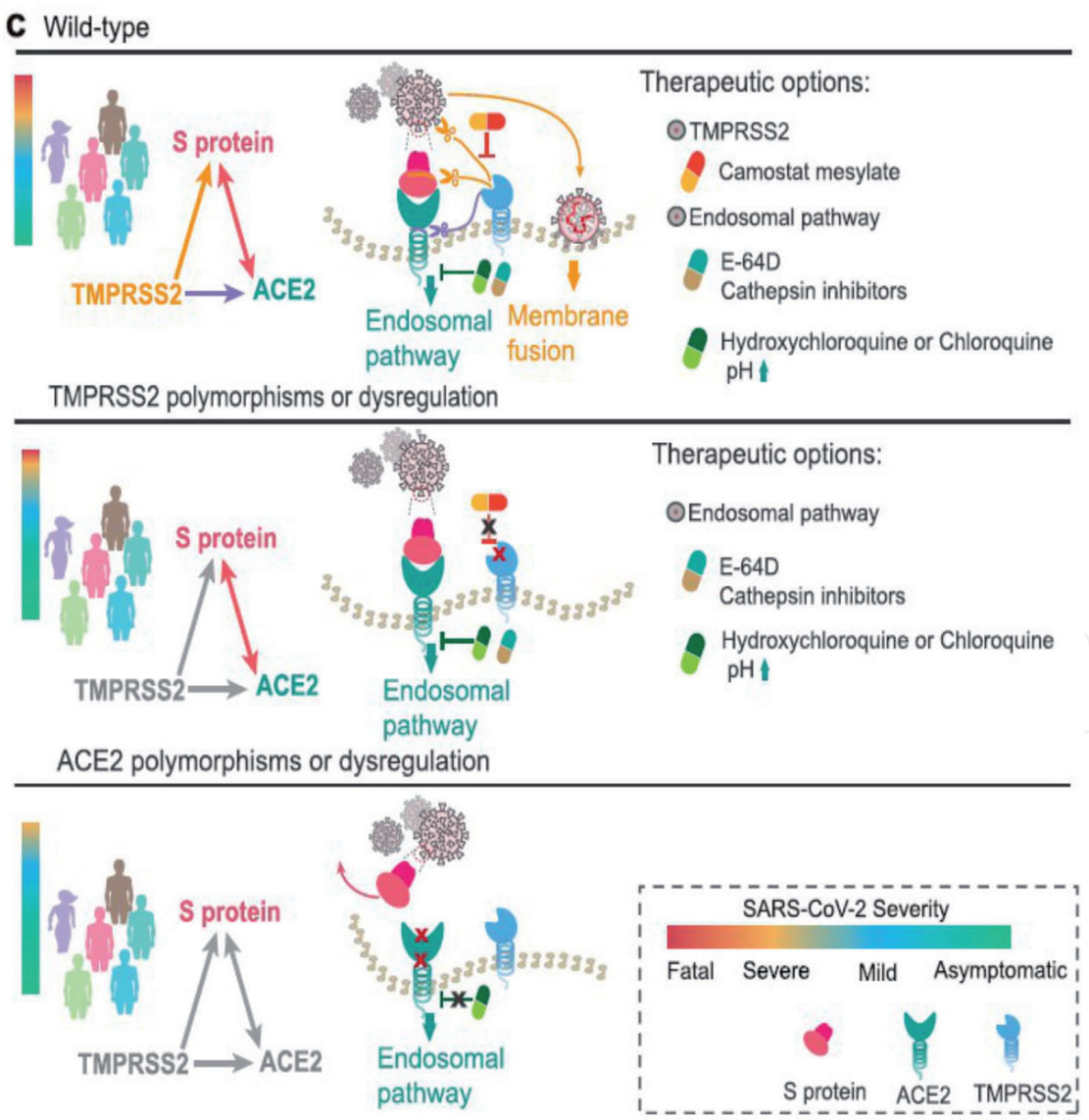

Figure 3.
A polymorphism and dysregulation of ACE2, and TMPRSS2 in COVID-19 and a suggested model for active compound medicines (e.g., hydroxychloroquine, Camostat mesylate, and E-64D [a protease inhibitor] for COVID-19) [93].

(G > A) were correlated with aggressive H7N9, H1N1, and increased lung expression of TMPRSS2 [92]. A study by Hou et al., indicated that 4% of nonidentical variants of TMPRSS2 are stop-codon mutations, Meanwhile, 59% are harmful mutations in TMPRSS2 coding regions [93]. The harmful variants (p.Arg240Cys, p.Val160Met, p.Gly181Arg, p.Pro335Leu, p.Gly432Ala, and p.Gly259Ser) in the coding region of TMPRSS2, are the same with somatic alterations arising in various types of cancer. In the same contest, Hou et al. found that, the p. Asp435Tyr which is a key site for catalytic residue binding of TMPRSS2 has unique low-frequency allele, but predominant SNPs in TMPRSS2 and offer possible descriptions for differential genetic infectivity to COVID-19 and for risk influences, such as those with tumor and male patients. By using the analysis of single-cell RNA-seq, Schuler et al. revealed that the expression of TMPRSS2 was upregulated in ciliated cells and alveolar epithelial type 1 cells and increased with humans aging [94]. This observation indicates that the developmental TMPRSS2 expression regulation may have a role in the relative protection of the children and infants from COVID-19 infection. Yet, it might be of great importance to investigate the link between TMPRSS2 polymorphisms and the age relationship with COVID-19 susceptibility (**Figure 3**).

7. Heme oxygenase-1 enzyme (HO-1) genetic polymorphisms and COVID-19 severity

Many studies demonstrated that the HO-1 gene polymorphisms, particularly the promoter region GT dinucleotide repeat mutation regulates the inducibility of HO-1 to ROS [95–101]. Subjects with more GT repeats have been believed to be more sensitive to cardiovascular endothelium diseases such as atherosclerosis coronary artery disease and aortic aneurysm s [95, 98, 99]. The lower Expression level of HO-1 in those with more GT repeats make the patients to be more affected to decrease endothelial hemostasis and inflammation [95–101]. While, GT sequences short alleles are correlated with increased HO-1 inducibility, which in turn reduced inflammation and enhanced cytoprotection [101]. Patients with COVID-19 complications perhaps have longer GT sequences and decreased vessel hemostasis.

COVID-19 disease has poor effects in diabetic and obese individuals, maybe because those people are already having high interleukin 6 levels of (IL-6) and they are in a proinflammatory state due to leptin and insulin resistance [102, 103]. As a result, the negative clinical outcomes of COVID-19 infection in obese patients was recorded [103]. Peterson et al. have revealed that obesity raises high-density lipoprotein (HDL) oxidation [104]. Oxidized HDL (Ox-HDL) is thought to produce pro-inflammatory cytokines by the direct action on adipocyte stem cells [105]. Ox-HDL initiates an inflammatory cascading with inflammatory cytokines, tumor necrosis factor (TNF), interleukins (IL-6, IL-1), and increasing of Angiotensin II (ANG II), a biomarker for early cardiovascular system disorders [104]. This made the obese individuals are more sensitive to heart failure due to infection of COVID-19 [106]. Up-regulation of HO-1-derived bilirubin may enhance the COVID-19 bad effect, this risk was reduced by an increased HO-1 level [107, 108]. Hence, up-regulation of the level of HO-1 with pharmacological treatment [109] may have valuable action in acute inflammation conditions.

8. BCL11A polymorphisms

BCL11A Genetic polymorphisms were correlating to produce fetal hemoglobin in overall population, and these genetic variants were later found to be able to

modify the severity of β-thalassemia and sickle cell diseases. Although the elevation of fetal hemoglobin can ameliorate the severity of these disorders. In an attempt to best comprehend the genetic background of this heterogeneity, genome-wide surveys were performed with 362,129 joint SNPs on a large cohort population of β-thalassemia and sickle cell patients to explore the genetic linking and relationship with HbF levels, in addition to other traits related to red blood cells. Among the principal variants influencing HbF levels, BCL11A SNP rs11886868 in the was completely correlated with this trait. This BCL11A variant was correlated with raised fetal hemoglobin (HbF) production in beta-thalassemia patients. Also, the similar BCL11A variants were substantially correlated with sickle cell patients HbF levels. These findings show that modifying HbF levels by BCL11A variants, consider as an essential factor in improving the beta-thalassemia phenotype and may potentially help improve other hemoglobin disorders. These findings can help describe the molecular mechanisms for regulating fetal globin and may ultimately participate in the evolution of new therapeutic strategies for sickle cell anemia and beta-thalassemia [110–112]. Hence, these results can provide an explanation of why some individuals naturally exhibit diseases mild symptoms, while others have shown very acute clinical symptoms. Therefore, it is imperative to perceive the role of genetic polymorphisms of these genes in SARS-CoV-2 infection in human populations to interpret the observed heterogeneity in predisposition and COVID-19 infection severity [88, 113].

9. Genetic polymorphism and therapy effectiveness

COVID-19 may be inactivated or partially treated by the following approaches: ACE2 receptor attaching site blocking either by antibody or specific ligand or using ACE2 soluble form that can neutralize the virus by binding the virus spike protein, and, yet, cover ACE2 binding site on the host cell surface and reducing the tissue injury. The genetic polymorphisms of cytochrome (CYP) 2D6 can affect drug metabolism using this approach, which contains 50% currently using drugs [114]. The metabolism of these genes can be increased by these polymorphisms and in turn, reduce their efficiency or significantly decline their metabolism causing drug toxicity [115]. Slow drug metabolizers permit toxic effects of the medications as chloroquine to become accumulated and resulting in cardiac problems with an increased hazard of cardiac arrest, specifically in diabetes and obesity patients. CYP2D6 Polymorphism is much high in Asians and African Americans [116–118], which extremely influenced by this disorder. One Korea study studying Lupus disease demonstrated considerable variation in the level of hydroxychloroquine due to polymorphisms of CYP2D6 [119]. This may explain the clinical outcomes differences when using this drug. Because of the metabolism abnormalities due to these genetic polymorphisms, resistant malaria strains will be arising [120–122]. Heart failure patients can be affected by the same CYP 2D6 gene polymorphisms since it is accountable for metoprolol metabolism [123, 124]. These gene variants affect several other medications such as barbiturates, Isoniazid (INH), serotonin reuptake inhibitor (omeprazole hydralazine sulfasalazine, etc.) [125]. Individuals with CYP2D6 polymorphisms and the HO-1 GT allele make therapy and disease outcomes challenging. Some of the patients who carry these polymorphisms will respond perfectly to drugs and have a low risk of COVID-19 patients to develop complications such as multiorgan failure and ARDS, while other patients will express drug toxicity levels and multiorgan problems [115]. This can describe why clinicians are unable to predict the multiorgan failure with COVID –19 disease and different outcomes from using 4-aminoquinolones.

10. Personalized medicine guided by host genetic of COVID-19

SARS-CoV-2 inhibition can be done by spike protein and ACE2 differential glycosylation [126]. Several polymorphisms, such as p.Pro389His, p.Met383Thr and p.Asp427Tyr slightly inhibited by hydroxychloroquine. This can be clarifying why hydroxychloroquine treatment was not significantly in a different hospital than others. [127]. However, more pharmacogenomics experiments between the genetic data and drug response from COVID-19 patients are extremely needed. The viral entry to the host cell by binding to the cell membrane through S protein can be blocked by TMPRSS2 [88]. The SARS-CoV-2 pathogenesis and infection depend on the TMPRSS2 presence, in a high pH environment [128, 129]. The inhibitor of endosomal acidification such as hydroxychloroquine and CatB/L inhibitors might work only in absence of TMPRSS2- in SARS-CoV-2 infected and may not work or has no or less effective in patients with TMPRSS2 wild-type [128]. So far, the populations with missense polymorphisms and stop-gained of TMPRSS2 polymorphisms may be good sensitive to treatment with hydroxychloroquine. Furthermore, the patients who carry TMPRSS2 and ACE2 wildtype, a mix of hydroxychloroquine or chloroquine with camostat may have the best clinical advantage. The ACE2 can be cleaved by TMPRSS2 at Arginine 697 to 716 [130], which improves viral entry. Thus, patients with, p.Arg710Cys p.Arg708Trp, p.Arg716Cys and p.Arg710His polymorphisms in ACE2 might have fewer symptoms of COVID-19 disease as the cleavage site of ACE2 gene loses by these polymorphisms (**Figure 3**) [113].

11. Conclusion

The pandemic COVID-19 by SARS-CoV-2 coronavirus is multifactorial in which human inheritances might play a pivotal role together with the co-morbidity diseases and other risk factors. The disease clinical course has been depending on the link between genetic variants, such as the CYP2D6 enzyme system, HO-1 (anti-inflammatory gene), and ACE-2 enzyme. Beside ACE2 polymorphisms, there is TMPRSS2 gene variance that possibly changes the pathogenicity of the virus by changing the interaction between ACE2 and SARS-CoV-2 virus. A good characterization of functional polymorphisms and the host genetics can assist in identifying the pathophysiology of the disease pathway to stratify the risk evaluation and to personalize the treatment procedures.

Conflict of interest

The authors declare no conflict of interest.

DOI: http://dx.doi.org/10.5772/intechopen.93676

Author details

Mahmood A. Al-Azzawi[1*] and Moustafa A. Sakr[2]

1 College of Dentistry, Al-Ayen University, An-Nasiriyah, Iraq

2 Genetic Engineering Institute, University of Sadat City, Sadat City, Egypt

*Address all correspondence to: mmahmood41@yahoo.com

References

[1] Anacleto O, Cabaleiro S, Villanueva B, et al. Genetic differences in host infectivity affect disease spread and survival in epidemics. Scientific Reports. 2019;**9**(1):4924. DOI: 10.1038/s41598-019-40567-w

[2] Bishop SC, Woolliams JA. Genomics and disease resistance studies in livestock. Livestock Science. 2014;**166**:190-198. DOI: 10.1016/j.livsci.2014.04.034

[3] Yáñez JM, Houston RD, Newman S. Genetics and genomics of disease resistance in salmonid species. Frontiers in Genetics. 2014;**5**:415. DOI: 10.3389/fgene.2014.00415

[4] O'Brien SJ, Evermann JF. Interactive influence of infectious disease and genetic diversity in natural populations. Trends in Ecology & Evolution. 1988;**3**(10):254-259. DOI: 10.1016/0169-5347(88)90058-4

[5] Doeschl-Wilson AB, Davidson R, Conington J, et al. Implications of host genetic variation on the risk and prevalence of infectious diseases transmitted through the environment. Genetics. 2011;**188**(3):683-693. DOI: 10.1534/genetics.110.125625

[6] King KC, Lively CM. Does genetic diversity limit disease spread in natural host populations? Heredity (Edinb.). 2012;**109**(4):199-203. DOI: 10.1038/hdy.2012.33

[7] Saura M, Carabaño MJ, Fernández A, et al. Disentangling genetic variation for resistance and endurance to scuticociliatosis in turbot using pedigree and genomic information. Frontiers in Genetics. 2019;**10**:539. DOI: 10.3389/fgene.2019.00539

[8] Kause A, Odegård J. The genetic analysis of tolerance to infections: A review. Frontiers in Genetics. 2012;**3**:262. DOI: 10.3389/fgene.2012.00262

[9] Gopinath S, Lichtman JS, Bouley DM, et al. Role of disease-associated tolerance in infectious superspreaders. Proceedings of the National Academy of Sciences of the United States of America. 2014;**111**:15780-15785. DOI: 10.1073/pnas.1409968111

[10] Wong G, Liu W, Liu Y, et al. MERS, SARS, and Ebola: The role of super-spreaders in infectious disease. Cell Host & Microbe. 2015;**18**(4):398-401. DOI: 10.1016/j.chom.2015.09.013

[11] Leavy O. Infectious disease: The tolerance of superspreaders. Nature Reviews. Immunology. 2014;**14**:776-777. DOI: doi.org/10.1038/nri3776

[12] Rauw WM. Immune response from a resource allocation perspective. Frontiers in Genetics. 2012;**3**:267. DOI: 10.3389/fgene.2012.00267

[13] Nath M, Woolliams JA, Bishop SC. Assessment of the dynamics of microparasite infections in genetically homogeneous and heterogeneous populations using a stochastic epidemic model. Journal of Animal Science. 2008;**86**:1747-1757. DOI: doi.org/10.2527/jas.2007-0615

[14] Karlsson EK, Kwiatkowski DP, Sabeti PC. Natural selection and infectious disease in human populations. Nature Reviews. Genetics. 2014;**15**(6):379-393. DOI: 10.1038/nrg3734

[15] Barreiro LB, Quintana-Murci L. From evolutionary genetics to human immunology: How selection shapes host defence genes. Nature Reviews. Genetics. 2010;**11**(1):17-30. DOI: 10.1038/nrg2698

[16] Houston RD. Future directions in breeding for disease resistance in aquaculture species. Revista Brasileira de Zootecnia. 2017;**46**(6):545-551. DOI: doi.org/10.1590/s1806-92902017000600010

[17] Lippi G, Sanchis-Gomar F, Henry BM. Coronavirus disease 2019 (COVID-19): The portrait of a perfect storm. Annals of Translational Medicine. 2020;**8**(7):497. DOI: 10.21037/atm.2020.03.157

[18] Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;**395**(10223):507-513. DOI: 10.1016/S0140-6736(20)30211-7

[19] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;**395**(10223):497-506. DOI: 10.1016/S0140-6736(20)30183-5

[20] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA; 2020;**323**(13):1239-1242. DOI: 10.1001/jama.2020.2648

[21] Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: Retrospective case series. BMJ. 2020;**368**:m606. DOI: 10.1136/bmj.m606

[22] Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;**395**(10229):1054-1062. DOI: 10.1016/S0140-6736(20)30566-3

[23] Velavan TP, Meyer CG. The Covid-19 epidemic. Tropical Medicine & International Health. 2020;**25**(3): 278-280. DOI: 10.1111/tmi.13383

[24] Nishiura H, Linton NM, Akhmetzhanov AR. Initial cluster of novel coronavirus (2019-nCoV) infections in Wuhan, China is consistent with substantial human-to-human transmission. Journal of Clinical Medicine. 2020;**9**(2):488. DOI: 10.3390/jcm9020488

[25] To KK, Tsang OT, Yip CC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clinical Infectious Diseases. 2020;**71**(15):841-843. DOI: 10.1093/cid/ciaa149

[26] Lin X, Gong Z, Xiao Z, et al. Novel coronavirus pneumonia outbreak in 2019: Computed tomographic findings in two cases. Korean Journal of Radiology. 2020;**21**(3):365-368. DOI: 10.3348/kjr.2020.0078

[27] Bastola A, Sah R, Rodriguez-Morales AJ, et al. The first 2019 novel coronavirus case in Nepal. The Lancet. Infectious Diseases. 2020;**20**(3):279-280. DOI: 10.1016/S1473-3099(20)30067-0

[28] Petrosillo N, Viceconte G, Ergonul O, et al. COVID-19, SARS and MERS: Are they closely related? Clinical Microbiology and Infection. 2020;**26**(6):729-734. DOI: 10.1016/j.cmi.2020.03.026

[29] Day M. Covid-19: Identifying and isolating asymptomatic people helped eliminate virus in Italian village. BMJ. 2020;**368**:m1165. DOI: 10.1136/bmj.m1165

[30] Lauretani F, Ravazzoni G, Roberti MF, et al. Assessment and treatment of older individuals with COVID 19 multi-system disease: Clinical and ethical implications. Acta Bio-Medica. 2020;**91**(2):150-168

[31] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;**323**(18):1775-1776. DOI: 10.1001/jama.2020.4683

[32] CDC Covid-Response Team. Severe outcomes among patients with coronavirus disease 2019 (COVID-19)—United States. MMWR. Morbidity and Mortality Weekly Report. 2020;**69**(12):343-346. DOI: 10.15585/mmwr.mm6912e2

[33] Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature. 2020;**584**(7821):430-436. DOI: 10.1038/s41586-020-2521-4

[34] Lippi G, Sanchis-Gomar F, Henry BM. Association between environmental pollution and prevalence of coronavirus disease 2019 (COVID-19) in Italy. medRxiv. 2020. DOI: 10.1101/2020.04.22.20075986

[35] Lippi G, Henry BM, Mattiuzzi C, et al. The death rate for COVID-19 is positively associated with gross domestic products. Acta Bio-Medica. 2020;**91**(2):224-225. DOI: 10.23750/abm.v91i2.9514

[36] Lippi G, Sanchis-Gomar F, Henry BM. Active smoking and COVID-19: A double-edged sword. European Journal of Internal Medicine. 2020;**77**:123-124. DOI: 10.1016/j.ejim.2020.04.060

[37] Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: A systematic review and meta-analysis. International Journal of Infectious Diseases. 2020;**94**:91-95. DOI: 10.1016/j.ijid.2020.03.017

[38] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Medicine and Infectious Disease. 2020;**34**:101623. DOI: 10.1016/j.tmaid.2020.101623

[39] Cascella M, Rajnik M, Cuomo A, et al. Features, evaluation and treatment coronavirus (COVID-19). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK554776/ [Updated: 04 July 2020]

[40] Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis. European Respiratory Journal. 2020;**55**(5):2000547. DOI: 10.1183/13993003.00547-2020

[41] Shang J, Ye G, Shi K, et al. Structural basis of receptor recognition by SARS-CoV-2. Nature. 2020;**581**(7807):221-224. DOI: 10.1038/s41586-020-2179-y

[42] Brielle ES, Schneidman-Duhovny D, Linial M. The SARS-CoV-2 exerts a distinctive strategy for interacting with the ACE2 human receptor. Viruses. 2020;**12**(5):497. DOI: 10.3390/v12050497

[43] Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. Viruses. 2012;**4**(6):1011-1033. DOI: 10.3390/v4061011

[44] Shang J, Wan Y, Luo C, et al. Cell entry mechanisms of SARS-CoV-2. Proceedings of the National Academy of Sciences of the United States of America. 2020;**117**(21):11727-11734. DOI: 10.1073/pnas.2003138117

[45] Walls AC, Park YJ, Tortorici MA, et al. Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 2020;**181**(2):281-292.e6. DOI: 10.1016/j.cell.2020.02.058

[46] Lambert DW, Yarski M, Warner FJ, et al. Tumor necrosis factor-alpha convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). Journal of Biological Chemistry. 2005;**280**(34):30113-30119. DOI: 10.1074/jbc.M505111200

[47] Rizzo P, Vieceli Dalla Sega F, Fortini F, et al. COVID-19 in the heart and the lungs: Could we "notch" the inflammatory storm? Basic Research in Cardiology. 2020;**115**(3):31. DOI: 10.1007/s00395-020-0791-5

[48] Fakhouri EW, Peterson SJ, Kothari J, et al. Genetic polymorphisms complicate COVID-19 therapy: Pivotal role of HO-1 in cytokine storm. Antioxidants. 2020;**9**(7):636. DOI: org/10.3390/antiox9070636

[49] Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infectious Diseases of Poverty. 2020;**9**(1):45. DOI: 10.1186/s40249-020-00662-x

[50] Sungnak W, Huang N, Bécavin C, et al. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nature Medicine. 2020;**26**(5):681-687. DOI: 10.1038/s41591-020-0868-6

[51] Xu H, Zhong L, Deng J, et al. High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science. 2020;**12**:8. DOI: 10.1038/s41368-020-0074-x

[52] Henry BM, de Oliveira MHS, Benoit S, et al. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): A meta-analysis. Clinical Chemistry and Laboratory Medicine. 2020;**58**(7):1021-1028. DOI: 10.1515/cclm-2020-0369

[53] Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 2005;**111**(20):2605-2610. DOI: 10.1161/CIRCULATIONAHA.104.510461

[54] Monteil V, Kwon H, Prado P, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell. 2020;**181**(4):905-913.e7. DOI: 10.1016/j.cell.2020.04.004

[55] Varga Z, Flammer AJ, Steiger P, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet. 2020;**395**(10234):1417-1418. DOI: 10.1016/S0140-6736(20)30937-5

[56] Taddei S, Virdis A, Ghiadoni L, et al. Effects of angiotensin converting enzyme inhibition on endothelium-dependent vasodilatation in essential hypertensive patients. Journal of Hypertension. 1998;**16**(4):447-456. DOI: 10.1097/00004872-199816040-00006

[57] Flammer AJ, Sudano I, Hermann F, et al. Angiotensin-converting enzyme inhibition improves vascular function in rheumatoid arthritis. Circulation. 2008;**117**(17):2262-2269. DOI: 10.1161/CIRCULATIONAHA.107.734384

[58] Hürlimann D, Forster A, Noll G, et al. Anti-tumor necrosis factor-alpha treatment improves endothelial function in patients with rheumatoid arthritis. Circulation. 2002;**106**(17):2184-2187. DOI: 10.1161/01.cir.0000037521.71373.44

[59] Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. Lancet.

2020;**395**(10234):1407-1409. DOI: 10.1016/S0140-6736(20)30858-8

[60] Leiden Open Variation Database. ACE2 Gene Homepage. Available from: https://databases.lovd.nl/shared/genes/ACE2 [Last accessed: 12 May 2020]

[61] Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. Cell Discovery. 2020;**6**:11. DOI: 10.1038/s41421-020-0147-1

[62] Peña Silva RA, Chu Y, Miller JD, et al. Impact of ACE2 deficiency and oxidative stress on cerebrovascular function with aging. Stroke. 2012;**43**(12):3358-3363. DOI: 10.1161/STROKEAHA.112.667063

[63] Tallant EA, Clark MA. Molecular mechanisms of inhibition of vascular growth by angiotensin-(1-7). Hypertension. 2003;**42**(4):574-579. DOI: 10.1161/01.HYP.0000090322.55782.30

[64] Crackower MA, Sarao R, Oudit GY, et al. Angiotensin-converting enzyme 2 is an essential regulator of heart function. Nature. 2002;**417**(6891):822-828. DOI: 10.1038/nature00786

[65] Díez-Freire C, Vázquez J, Correa de Adjounian MF, et al. ACE2 gene transfer attenuates hypertension-linked pathophysiological changes in the SHR. Physiological Genomics. 2006;**27**(1):12-19. DOI: 10.1152/physiolgenomics.00312.2005

[66] Tikellis C, Pickering R, Tsorotes D, et al. Interaction of diabetes and ACE2 in the pathogenesis of cardiovascular disease in experimental diabetes. Clinical Science (London). 2012;**123**(8):519-529. DOI: 10.1042/CS20110668

[67] Niu W, Qi Y, Hou S, et al. Correlation of angiotensin-converting enzyme 2 gene polymorphisms with stage 2 hypertension in Han Chinese. Translational Research. 2007;**150**(6):374-380. DOI: 10.1016/j.trsl.2007.06.002

[68] Fan XH, Wang YB, Wang H, et al. Polymorphisms of angiotensin-converting enzyme (ACE) and ACE2 are not associated with orthostatic blood pressure dysregulation in hypertensive patients. Acta Pharmacologica Sinica. 2009;**30**(9):1237-1244. DOI: 10.1038/aps.2009.110

[69] Chen YY, Liu D, Zhang P, et al. Impact of ACE2 gene polymorphism on antihypertensive efficacy of ACE inhibitors. Journal of Human Hypertension. 2016;**30**(12):766-771. DOI: 10.1038/jhh.2016.24

[70] Luo Y, Liu C, Guan T, et al. Association of ACE2 genetic polymorphisms with hypertension-related target organ damages in south. Hypertension Research. 2019;**42**(5):681-689. DOI: 10.1038/s41440-018-0166-6

[71] Chen Q, Tang X, Yu CQ, et al. Correlation of angiotensin-converting enzyme 2 gene polymorphism with antihypertensive effects of benazepril. Beijing Da Xue Xue Bao. Yi Xue Ban. 2010;**42**(3):293-298

[72] Patnaik M, Pati P, Swain SN, et al. Association of angiotensin-converting enzyme and angiotensin-converting enzyme-2 gene polymorphisms with essential hypertension in the population of Odisha, India. Annals of Human Biology. 2014;**41**(2):145-152. DOI: 10.3109/03014460.2013.837195

[73] Pinheiro DS, Santos RS, Jardim PCBV, et al. The combination of ACE I/D and ACE2 G8790A polymorphisms revels susceptibility to hypertension: A genetic association study in Brazilian patients. PLOS One. 2019;**14**(8):e0221248. DOI: 10.1371/journal.pone.0221248

[74] Duru K, Farrow S, Wang JM, et al. Frequency of a deletion polymorphism in the gene for angiotensin converting enzyme is increased in African-Americans with hypertension. American Journal of Hypertension. 1994;**7**(8):759-762. DOI: 10.1093/ajh/7.8.759

[75] Devaux CA, Rolain JM, Raoult D. ACE2 receptor polymorphism: Susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. Journal of Microbiology, Immunology, and Infection. 2020;**53**(3):425-435. DOI: 10.1016/j.jmii.2020.04.015

[76] Babcock GJ, Esshaki DJ, Thomas WD Jr, et al. Amino acids 270 to 510 of the severe acute respiratory syndrome coronavirus spike protein are required for interaction with receptor. Journal of Virology. 2004;**78**(9):4552-4560. DOI: 10.1128/jvi.78.9.4552-4560.2004

[77] Xiao F, Zimpelmann J, Agaybi S, et al. Characterization of angiotensin-converting enzyme 2 ectodomain shedding from mouse proximal tubular cells. PLOS One. 2014;**9**(1):e85958. DOI: 10.1371/journal.pone.0085958

[78] Glowacka I, Bertram S, Herzog P, et al. Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. Journal of Virology. 2010;**84**(2):1198-1205. DOI: 10.1128/JVI.01248-09

[79] Chen J, Jiang Q, Xia X, et al. Individual variation of the SARS-CoV-2 receptor ACE2 gene expression and regulation. Aging Cell. 2020;**19**(7);e13168. DOI: 10.1111/acel.13168

[80] Hussain M, Jabeen N, Raza F, et al. Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike. Journal of Medical Virology. 2020. DOI: 10.1002/jmv.25832

[81] Stawiski EW, Diwanji D, Suryamohan K, et al. Human ACE2 receptor polymorphisms predict SARS-CoV-2 susceptibility. bioRxiv. 2020; 2020.04.07.024752. DOI:10.1101/2020.04.07.024752

[82] Benetti E, Tita R, Spiga O, et al. ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. European Journal of Human Genetics. 2020:1-13. DOI: 10.1038/s41431-020-0691-z

[83] Chiu RW, Tang NL, Hui DS, et al. ACE2 gene polymorphisms do not affect outcome of severe acute respiratory syndrome. Clinical Chemistry. 2004;**50**(9):1683-1686. DOI: 10.1373/clinchem.2004.035436

[84] Li G, He X, Zhang L, et al. Assessing ACE2 expression patterns in lung tissues in the pathogenesis of COVID-19. Journal of Autoimmunity. 2020;**112**:102463. DOI: 10.1016/j.jaut.2020.102463

[85] Yang M, Zhao J, Xing L, et al. The association between angiotensin-converting enzyme 2 polymorphisms and essential hypertension risk: A meta-analysis involving 14,122 patients. Journal of the Renin-Angiotensin-Aldosterone System. 2015;**16**(4):1240-1244. DOI: 10.1177/1470320314549221

[86] Liu D, Chen Y, Zhang P, et al. Association between circulating levels of ACE2-Ang-(1-7)-MAS axis and ACE2 gene polymorphisms in hypertensive patients. Medicine (Baltimore). 2016;**95**(24):e3876. DOI: 10.1097/MD.0000000000003876

[87] Gemmati D, Bramanti B, Serino ML, et al. COVID-19 and individual genetic susceptibility/receptivity: Role of ACE1/ACE2 genes, immunity, inflammation and coagulation. Might the double X-chromosome in females be protective against SARS-CoV-2 compared to

the single X-chromosome in males. International Journal of Molecular Sciences. 2020;**21**(10):3474. DOI: 10.3390/ijms21103474

[88] Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;**181**(2):271-280.e8. DOI: 10.1016/j.cell.2020.02.052

[89] Luostari K, Hartikainen JM, Tengstrom M, et al. Type II transmembrane serine protease gene variants associate with breast cancer. PLOS One. 2014;**9**(7):e102519. DOI: 10.1371/journal.pone.0102519

[90] FitzGerald LM, Agalliu I, Johnson K, et al. Association of TMPRSS2-ERG gene fusion with clinical characteristics and outcomes: Results from a population-based study of prostate cancer. BMC Cancer. 2008;**8**:230. DOI: 10.1186/1471-2407-8-230

[91] Giri VN, Ruth K, Hughes L, et al. Racial differences in prediction of time to prostate cancer diagnosis in a prospective screening cohort of high-risk men: Effect of TMPRSS2 Met160Val. BJU International. 2011;**107**(3):466-470. DOI: 10.1111/j.1464-410X.2010.09522.x

[92] Cheng Z, Zhou J, To KK, et al. Identification of TMPRSS2 as a susceptibility gene for severe 2009 pandemic A(H1N1) influenza and A(H7N9) influenza. The Journal of Infectious Diseases. 2015;**212**(8): 1214-1221. DOI: 10.1093/infdis/jiv246

[93] Hou Y, Zhao J, Martin W, et al. New insights into genetic susceptibility of COVID-19: An ACE2 and TMPRSS2 polymorphism analysis. BMC Medicine. 2020;**18**(1):216. DOI: 10.1186/s12916-020-01673-z

[94] Schuler BA, Habermann AC, Plosa EJ, et al. Age-related expression of SARS-CoV-2 priming protease TMPRSS2 in the developing lung. Biorxiv: The Preprint Server for Biology. 2020. DOI: 10.1101/2020.05.22.111187

[95] Pechlaner R, Willeit P, Summerer M, et al. Heme oxygenase-1 gene promoter microsatellite polymorphism is associated with progressive atherosclerosis and incident cardiovascular disease. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;**35**(1):229-236. DOI: 10.1161/ATVBAHA.114.304729

[96] Yamada N, Yamaya M, Okinaga S, et al. Microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with susceptibility to emphysema. American Journal of Human Genetics. 2000;**66**(1):187-195. DOI: 10.1086/302729

[97] Okamoto I, Krögler J, Endler G, et al. A microsatellite polymorphism in the heme oxygenase-1 gene promoter is associated with risk for melanoma. International Journal of Cancer. 2006;**119**(6):1312-1315. DOI: 10.1002/ijc.21937

[98] Hirai H, Kubo H, Yamaya M, et al. Microsatellite polymorphism in heme oxygenase-1 gene promoter is associated with susceptibility to oxidant-induced apoptosis in lymphoblastoid cell lines. Blood. 2003;**102**(5):1619-1621. DOI: 10.1182/blood-2002-12-3733

[99] Guénégou A, Leynaert B, Bénessiano J, et al. Association of lung function decline with the heme oxygenase-1 gene promoter microsatellite polymorphism in a general population sample. Results from the European Community Respiratory Health Survey (ECRHS), France. Journal of Medical Genetics. 2006;**43**(8):e43. DOI: 10.1136/jmg.2005.039743

[100] Exner M, Schillinger M, Minar E, et al. Heme oxygenase-1 gene

promoter microsatellite polymorphism is associated with restenosis after percutaneous transluminal angioplasty. Journal of Endovascular Therapy. 2001;**8**(5):433-440. DOI: 10.1177/152660280100800501

[101] Bao W, Song F, Li X, et al. Association between heme oxygenase-1 gene promoter polymorphisms and type 2 diabetes mellitus: A HuGE review and meta-analysis. American Journal of Epidemiology. 2010;**172**(6):631-636. DOI: 10.1093/aje/kwq162

[102] Zhou Y, Rui L. Leptin signaling and leptin resistance. Frontiers of Medicine. 2013;**7**(2):207-222. DOI: 10.1007/s11684-013-0263-5

[103] Peterson SJ, Dave N, Kothari J. The effects of heme oxygenase upregulation on obesity and the metabolic syndrome. Antioxidants & Redox Signaling. 2020;**32**(14):1061-1070. DOI: 10.1089/ars.2019.7954

[104] Peterson SJ, Shapiro JI, Thompson E, et al. Oxidized HDL, adipokines, and endothelial dysfunction: A potential biomarker profile for cardiovascular risk in women with obesity. Obesity (Silver Spring). 2019;**27**(1):87-93. DOI: 10.1002/oby.22354

[105] Peterson SJ, Vanella L, Bialczak A, et al. Oxidized HDL and isoprostane exert a potent adipogenic effect on stem cells: Where in the lineage? Journal of Cell, Stem cells and Regenerative Medicine. 2016;**2**(1). DOI: 10.16966/2472-6990.109

[106] Aghagoli G, Gallo Marin B, Soliman LB, et al. Cardiac involvement in COVID-19 patients: Risk factors, predictors, and complications: A review. Journal of Cardiac Surgery. 2020;**35**(6):1302-1305. DOI: 10.1111/jocs.14538

[107] Singh SP, McClung JA, Thompson E, et al. Cardioprotective heme oxygenase-1-PGC1α signaling in epicardial fat attenuates cardiovascular risk in humans as in obese mice. Obesity (Silver Spring). 2019;**27**(10):1634-1643. DOI: 10.1002/oby.22608

[108] Peterson SJ, Yadav R, Iacobellis G. Cardioprotective heme oxygenase 1-PGC1α signaling in epicardial fat attenuates cardiovascular risk in humans as in obese mice. Obesity (Silver Spring). 2019;**27**(10):1560-1561. DOI: 10.1002/oby.22629

[109] Peterson SJ, Rubinstein R, Faroqui M, et al. Positive effects of heme oxygenase upregulation on adiposity and vascular dysfunction: Gene targeting vs. pharmacologic therapy. International Journal of Molecular Sciences. 2019;**20**(10):2514. DOI: 10.3390/ijms20102514

[110] Menzel S, Garner C, Gut I, et al. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. Nature Genetics. 2007;**39**(10):1197-1199. DOI: 10.1038/ng2108

[111] Lettre G, Sankaran VG, Bezerra MA, et al. DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(33):11869-11874. DOI: 10.1073/pnas.0804799105

[112] Uda M, Galanello R, Sanna S, et al. Genome-wide association study shows BCL11A associated with persistent fetal hemoglobin and amelioration of the phenotype of beta-thalassemia. Proceedings of the National Academy of Sciences of the United States of America. 2008;**105**(5):1620-1625. DOI: 10.1073/pnas.0711566105

[113] Yan R, Zhang Y, Li Y, et al. Structural basis for the recognition

of SARS-CoV-2 by full-length human ACE2. Science. 2020;**367**(6485):1444-1448. DOI: 10.1126/science.abb2762

[114] Ingelman-Sundberg M. Genetic polymorphisms of cytochrome P450 2D6 (CYP2D6): Clinical consequences, evolutionary aspects and functional diversity. The Pharmacogenomics Journal. 2005;**5**(1):6-13. DOI: 10.1038/sj.tpj.6500285

[115] Haertter S. Recent examples on the clinical relevance of the CYP2D6 polymorphism and endogenous functionality of CYP2D6. Drug Metabolism and Drug Interactions. 2013;**28**(4):209-216. DOI: 10.1515/dmdi-2013-0032

[116] Wan YJ, Poland RE, Han G, et al. Analysis of the CYP2D6 gene polymorphism and enzyme activity in African-Americans in southern California. Pharmacogenetics. 2001;**11**(6):489-499. DOI: 10.1097/00008571-200108000-00004

[117] Yee MM, Josephson C, Hill CE, et al. Cytochrome P450 2D6 polymorphisms and predicted opioid metabolism in African American children with sickle cell disease. Journal of Pediatric Hematology/Oncology. 2013;**35**(7):e301-e305. DOI: 10.1097/MPH.0b013e31828e52d2

[118] Gaedigk A, Bhathena A, Ndjountché L, et al. Identification and characterization of novel sequence variations in the cytochrome P4502D6 (CYP2D6) gene in African Americans. The Pharmacogenomics Journal. 2005;**5**(3):173-182. DOI: 10.1038/sj.tpj.6500305 [published correction appears in Pharmacogenomics J. 2005;5(4):276. Rogan, PK (added)]

[119] Lee JY, Vinayagamoorthy N, Han K, et al. Association of polymorphisms of cytochrome P450 2D6 with blood hydroxychloroquine levels in patients with systemic lupus erythematosus. Arthritis & Rheumatology. 2016;**68**(1):184-190. DOI: 10.1002/art.39402

[120] He X, Pan M, Zeng W, et al. Multiple relapses of plasmodium vivax malaria acquired from West Africa and association with poor metabolizer CYP2D6 variant: A case report. BMC Infectious Diseases. 2019;**19**(1):704. DOI: 10.1186/s12879-019-4357-9

[121] Haraya K, Kato M, Chiba K, et al. Prediction of inter-individual variability on the pharmacokinetics of CYP2C8 substrates in human. Drug Metabolism and Pharmacokinetics. 2017;**32**(6):277-285. DOI: 10.1016/j.dmpk.2017.09.001

[122] Silvino AC, Costa GL, Araújo FC, et al. Variation in human cytochrome P-450 drug-metabolism genes: A gateway to the understanding of plasmodium vivax relapses. PLOS One. 2016;**11**(7):e0160172. DOI: 10.1371/journal.pone.0160172

[123] Wang B, Yang LP, Zhang XZ, et al. New insights into the structural characteristics and functional relevance of the human cytochrome P450 2D6 enzyme. Drug Metabolism Reviews. 2009;**41**(4):573-643. DOI: 10.1080/03602530903118729

[124] Mottet F, Vardeny O, de Denus S. Pharmacogenomics of heart failure: A systematic review. Pharmacogenomics. 2016;**17**(16):1817-1858. DOI: 10.2217/pgs-2016-0118

[125] Zhao RZ, Jiang S, Zhang L, et al. Mitochondrial electron transport chain, ROS generation and uncoupling (review). International Journal of Molecular Medicine. 2019;**44**(1):3-15. DOI: 10.3892/ijmm.2019.4188

[126] Savarino A, Di Trani L, Donatelli I, et al. New insights into the antiviral effects of chloroquine. The Lancet. Infectious Diseases. 2006;**6**(2):67-69. DOI: 10.1016/S1473-3099(06)70361-9

[127] Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. Journal of the American Medical Association. 2020;**323**(24):2493-2502. DOI: 10.1001/jama.2020.8630

[128] Shulla A, Heald-Sargent T, Subramanya G, et al. A transmembrane serine protease is linked to the severe acute respiratory syndrome coronavirus receptor and activates virus entry. Journal of Virology. 2011;**85**(2):873-882

[129] Simmons G, Gosalia DN, Rennekamp AJ, et al. Inhibitors of cathepsin L prevent severe acute respiratory syndrome coronavirus entry. Proceedings of the National Academy of Sciences of the United States of America. 2005;**102**(33):11876-11881. DOI: 10.1073/pnas.0505577102

[130] Heurich A, Hofmann-Winkler H, Gierer S, et al. TMPRSS2 and ADAM17 cleave ACE2 differentially and only proteolysis by TMPRSS2 augments entry driven by the severe acute respiratory syndrome coronavirus spike protein. Journal of Virology. 2014;**88**(2):1293-1307. DOI: 10.1128/JVI.02202-13