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REVIEW

Human gene polymorphisms and their possible impact on the clinical outcome of SARS-CoV-2 infection

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Abstract

The SARS-CoV-2 pandemic has become one of the most serious health concerns globally. Although multiple vaccines have recently been approved for the prevention of coronavirus disease 2019 (COVID-19), an effective treatment is still lacking. Our knowledge of the pathogenicity of this virus is still incomplete. Studies have revealed that viral factors such as the viral load, duration of exposure to the virus, and viral mutations are important variables in COVID-19 outcome. Furthermore, host factors, including age, health condition, co-morbidities, and genetic background, might also be involved in clinical manifestations and infection outcome. This review focuses on the importance of variations in the host genetic background and pathogenesis of SARS-CoV-2. We will discuss the significance of polymorphisms in the ACE-2, TMPRSS2, vitamin D receptor, vitamin D binding protein, CD147, glucose-regulated protein 78 kDa, dipeptidyl peptidase-4 (DPP4), neuropilin-1, heme oxygenase, apolipoprotein L1, vitamin K epoxide reductase complex 1 (VKORC1), and immune system genes for the clinical outcome of COVID-19.

Background

In March 2020, the World Health Organization (WHO) declared a pandemic caused by an emerging coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The pathogen rapidly surged across the globe, causing havoc on all continents and severely destabilizing healthcare systems. An infection with this virus can cause a variety of mild to severe symptoms, which are collectively named coronavirus disease-2019 (COVID-19) [1]. SARS-CoV-2 is a member of the genus *Betacoronavirus*, family *Coronaviridae*. This enveloped virus has a positive single-stranded RNA genome with a length of 29.8 to 29.9 kb, making it the largest amongst all human RNA viruses [2–4]. SARS-CoV-2 is primarily transmitted through respiratory droplets and contact routes [2, 5]. With unprecedented speed, multiple vaccines have recently been approved, and many others are currently under development

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to prevent COVID-19. However, with regard to antiviral drugs, specific treatments for SARS-CoV-2 are not yet available.

The course of disease can differ greatly among individuals, ranging from an asymptomatic infection to mild or severe disease and death. The mortality rate for SARS-CoV-2 is still under debate and is affected by multiple variables [2, 5–7]. From the start of the COVID-19 pandemic, there have been numerous publications about the pathogenesis of the virus, but much still remains to be elucidated. For instance, it is still not clear why some people remain asymptomatic while others develop severe disease. Furthermore, viral respiratory infections are usually more serious in children than in adults, but for SARS-CoV-2 infection this seems to be reversed. Answering these questions and finding the factors that affect the virulence of SARS-CoV-2 will contribute to the development of suitable treatment strategies and better infection control.

Age is an important factor in the outcome of viral respiratory infections. During the Spanish flu pandemic in 1918, the mean death rate was high in people aged younger than five years, 20-40 years old, and older than 65 years [8]. Similarly, at the start of the H1N1 influenza pandemic in 2009, severe pneumonia was observed in 5- to 59-year-old individuals [9]. With other coronaviruses, such as SARS-CoV and human cronavirus-NL63 (HCoV-NL63), it has been observed that children are relatively resistant to infection, similar to the current observations for SARS-CoV-2 [10, 11].

It has been demonstrated that viral factors such as the number of viral particles in the inoculum, duration of exposure to the virus, and mutations in the virus genome can influence the severity and outcome of the disease [12]. Similarly, host factors such as health condition, age, gender, smoking, immune status, diabetes, hypertension, cardiovascular disease, chronic respiratory disease, cancer, and, more importantly, the genetic background, might determine the clinical manifestations and outcome of infection [13–17]. Based on the data, it appears that the genetic background of the host influences the severity of the infection and disease outcome [18, 19]. In this review, we provide a comprehensive overview of the current data regarding host gene polymorphisms that might be associated with the pathogenesis and outcome of SARS-CoV-2 infection.

Angiotensin-converting enzyme 1 and angiotensin-converting enzyme 2 polymorphisms

The human ACE or ACE-1 gene is located on chromosome 17q23.3 and is made up of 26 exons. It contains some polymorphisms including insertions (I) or deletions (D) as well as a repetitive sequence of 287 base pairs of Alu sequence in intron 16 [20]. It has been reported that polymorphisms in this gene are associated with SARS-CoV infection outcome [21]. The serum level of ACE in people with the DD genotype is almost twice that of genotype II [22]. The D allele might affect renin-angiotensin pathway activity by increasing the serum or local level of ACE, leading to damage of the vascular endothelium and lung epithelium [23]. Studies have shown that some ACE polymorphisms are associated with Alzheimer's disease (the II and ID ACE genotypes), cardiovascular disease (DD), hepatitis C virus (HCV) infection (DD), and cancers (ACE A240T polymorphism) [24–29] (Table 1). Itoyama et al. found that the frequency of the D allele in SARS patients (with and without hypoxemia) was significantly higher than in healthy controls [21]. Also, they suggested that ACE-1 insertions/deletions (I/D) could probably accelerate the development of pneumonia in SARS-CoV infection [21]. Another study in Caucasian individuals demonstrated that the presence of the D allele was accompanied by an increased rate of acute respiratory distress syndrome (ARDS) [30]. Yamamoto et al. reported that the frequency of SARS-CoV-2 infections and mortality strongly correlated with the ACE-1 I/D genotype, which might serve as a predictive marker for the severity of COVID-19 [31]. On the other hand, Chan et al. reported that in the Chinese population, the ACE I/D polymorphism was not associated with SARS-CoV infection [32] (Table 2). The reason for this discrepancy in the Chinese population is unknown, but it might be related to the lower frequency of the DD genotype and the D allele in the Chinese population than in people with a Caucasian background [30, 33].

Angiotensin-converting enzyme 2 (ACE-2) is a close homolog of ACE (or ACE-1), exhibiting 61% amino acid similarity and 40% sequence identity. ACE-2 acts as a carboxyl peptidase [34] and has been recognized as the main entry receptor for both SARS-CoV and SARS-CoV-2 through interaction with the spike (S) protein [35]. The ACE-2 gene is located on chromosome Xp22.2 and contains 18 exons [36]. This enzyme is anchored in the cell membranes as a type 1 integral membrane glycoprotein with a high expression level in lung, heart, artery, intestinal, and kidney tissues [37]. The primary role of ACE-2 is converting angiotensin II to angiotensin 1-7, but it also converts angiotensin I to angiotensin 1-9 [34]. Aberrant expression of ACE-2 has been associated with atherosclerosis, hypertension, heart failure, chronic kidney disease, and increased vascular permeability, facilitating respiratory system edema [38–43].

Entry of SARS-CoV-2 into target cells is facilitated by the S protein, which consists of two subunits, S1 and S2. The S1 subunit contains the receptor-binding domain (RBD), which interacts with the peptidase domain (PD) of the ACE-2 protein, and this is a critical step for entry of the virus into the host cell [44]. Therefore, genetic variations in the ACE-2

sequence might alter the molecular interaction of the RBD and PD domains, which not only changes the host susceptibility to the virus but also influences the severity of the disease and the outcome of infection.

A recent investigation indicated that genetic variations and expression patterns of ACE-2 might reduce susceptibility to SARS-CoV-2 infection. Given that ACE-2 is located on sex chromosome X, it could be related to the observed gender discrepancies in disease outcome. Srivastava et al. reported a significant positive correlation between ACE2 rs2285666 polymorphism and a lower frequency of infection and case-fatality rate in SARS-CoV-2 infection in the Indian population [45]. Moreover, it has been reported that three SNPs – K26R (rs4646116), M82I (rs267606406) and E329G (rs143936283) – are associated with higher binding affinity for the RBD domain of the S protein compared to wild-type ACE-2. This might result in increased susceptibility to SARS-CoV-2 infection [46]. In contrast, the I21T (rs1244687367), E37K (rs146676783) and D355N (rs961360700) SNPs cause a significantly lower binding affinity and could decrease the susceptibility to infection [46]. Moreover, the hotspot N720D variant in the C-terminal collectrin-like domain of ACE-2 affects the ACE-2-TMPRSS2 complex and creates a favorable site for TMPRSS2 binding and cleavage, thus facilitating binding to the S protein and potentially promoting virus entry into the cell [47]. Molecular docking simulations have revealed that six ACE2 *missense* variants – I21T, A25T, K26R, E75G, T55A and E37K – increase binding affinity, while 11 variants – I21V, E35K, K26E, T27A, S43R, Y50F, N51D, N58H, K68E, E23K and M82I – decrease the affinity of ACE-2 for the RBD of the S protein [48]. Hashizume et al. reported that ACE-2 SNPs have a limited impact on the ACE-2-dependent cell entry of SARS-CoV-2 [49]. Furthermore, a large cohort study on an Italian population demonstrated no significant relationship between ACE-2 polymorphisms and the severity of COVID-19 [15] (Table 2).

Both SARS-CoV and human coronavirus NL-63 replication cause a reduction in the expression of the ACE-2 protein, which has been demonstrated to induce more-severe complications in SARS-CoV infection [50]. This reduction is caused by the inhibitory effect of the S protein on ACE-2 expression in infected cells and might result in severe acute lung failure [50]. Hence, considering the protective function of ACE-2 in the tissues, SARS-CoV-2 infections might induce an imbalance in Ang II/Ang1-7 and consequently result in inflammation and hypoxia [51]. Another report has indicated that an increase in the concentration and/or expression of ACE-2 receptors in pediatric lung pneumocytes probably provides protection against severe clinical manifestations of SARS-CoV-2 infection [52]. It has been shown that the injection of the SARS-CoV S protein into mice leads to pulmonary failure. This effect was diminished by blocking the renin-angiotensin pathway [53]. Angiotensin II type I receptor (AT1R) is an important receptor that mediates vascular permeability, and its activation promotes severe acute pulmonary damage [54]. A study performed in mice demonstrated that the inhibition of AT1R reduces severe lung damage as well as pulmonary edema [53].

In addition to its involvement in coronavirus infection, ACE-2 has also been associated with other viral respiratory infections. For instance, Gu et al. reported that ACE-2 plays a considerable role in pulmonary damage related to respiratory syncytial virus (RSV) infection, which might be related to the high level of angiotensin II in the plasma [55]. Increased levels of angiotensin II could be the result of decreased ACE-2 expression and could lead to severe lung damage by mediating AT1R during RSV infection [55]. Moreover, an association was observed between influenza virus infection and ACE-2 expression levels, which was different with various strains of influenza virus [56, 57]. Although some studies have focused on studying pulmonary pathology to evaluate the impact of these viruses, the molecular mechanisms by which one is predisposed to pulmonary damage are not completely explained by the effects of infection on the renin–angiotensin system (RAS) and ACE-2.

Transmembrane protease serine 2 polymorphism

The transmembrane protease serine 2 (TMPRSS2) gene, with a length of 43.59 kbp, is located on chromosome 21q22.3 and consists of 14 exons [58]. It encodes a transcript that is processed by alternative splicing to provide two mRNA variants of 3.25 and 3.21 kb. The TMPRSS2 protein (492 amino acids) is a type II transmembrane serine protease that is expressed on the surface of different tissues/cells, including the small intestine, prostate, colon, salivary gland, and stomach [58]. TMPRSS2 upregulation has been demonstrated in some cancerous cells, and it promotes metastasis by proteolytic activation of hepatocyte growth factor (HGF), a pathway that is targeted by specific drugs [59]. Some polymorphisms in TMPRSS2 have been reported to be genetic risk factors for specific types of cancers and viral infections [15, 60]. For instance, the TMPRSS2 M160V polymorphism increases the susceptibility to prostate cancer in Japanese men [60].

Recently, it was reported that polymorphisms in the TMPRSS2 gene might be involved in susceptibility to SARS-CoV-2 infection and COVID-19 outcome [15]. Proteolytic cleavage of the S protein by TMPRSS2 at the S1/S2 boundary triggers S2-mediated fusion of the viral envelope and endosome membrane, which is a crucial step for the release of the ribonucleoprotein into the cytoplasm [35]. Expression of the TMPRSS2 gene is

Table 1 Human genetic polymorphisms related to the outcome of infection with other CoVs as well as non-CoVs

Gene	Location	Functions	Polymorphisms	Outcomes	References
Involved in virus attachment and entry					
ACE	Xp22.2	a) Converts angiotensin I to angiotensin 1-9	D/D	Associated with HCV infection, but not with the progression or degree of hepatic fibrosis	Mackawy et al. 2012 [28]
			D allele	Development of pneumonia in SARS-CoV-1 infection	Itoyama et al. 2004 [21]
		b) Converts angiotensin II to angiotensin 1-7	D/D	Susceptibility and outcome in acute respiratory distress syndrome (ARDS)	Marshall et al. 2002 [30]
TMPRSS2	21q22.3	Transmembrane serine protease	rs2070788 and rs383510	Associated with higher susceptibility to H1N1 and H7N9 infection	Cheng et al. 2015 [65]
Involved in immune system responses					
OAS1	12q24.13	Member of the 2′–5′-OAS gene family that is induced by IFN and interferes with viral replication	A/G SNP at the 3'UTR 347 locus	G allele confers protection against SARS-CoV-1 infection	He et al. 2006 [90]
MxA or Mx1	21q22.3	Involved in the cellular antiviral response (different RNA and DNA viruses)	G/T polymorphism at position 88 in the MxA gene promoter region	GT genotype increases the expression of MxA protein and promotes persistent SARS-CoV-1 infection	He et al. 2006 [90]
			−123(C/A) and −88(G7T)	Affects the levels of protein expression, thereby influencing the disease outcome in patients with HBV, HCV as well as enterovirus 71 and SARS-CoV-1 infection	Cao et al. 2009 [91] Hamano et al. 2005 [93] Hijikata et al. 2000 [94] Knapp et al. 2003 [95] Kong et al. 2007 [96] Suzuki et al. 2004 [97] Zhang et al. 2014 [98]
CD14	5q31.3	Cell differentiation, host-pathogen interactions and a key molecule in the activation of the innate immune cells	159CC polymorphism (rs2569190)	Significantly higher in patients suffering from severe SARS-CoV-1 infection	Yuan et al. 2007 [99]
MBL	10q21.1	Recognizes and binds to mannose and N-acetylglucosamine on microorganisms, including yeast, bacteria, and viruses (influenza virus, SARS-CoV and HIV)	rs1800450	Associated with the risk of SARS-CoV-1 infection	Tu et al. 2015 [101]
CCL2	17q12	A chemotactic activity for basophils and monocytes	rs1024611	Associated with the risk of SARS-CoV-1 infection	Tu et al. 2015 [100]
CD209 or DC-SIGN	19p13.2	Innate immunity and antiviral defense	G allele in rs10518270 and rs2335525	A risk allele in SARS-CoV-1 infection	Iyer et al. 2020 [106]
IL6	7p15.3	Involved in B cell maturation and inflammation	174 C/C genotype in rs1800795	Severe RSV infection Related to higher cytokine production and pneumonia severity	Doyle et al. 2010 [71] Ulhaq et al. 2020 [72]

Table 1 (continued)

Gene	Location	Functions	Polymorphisms	Outcomes	References
HLA	6p21	Key roles in the immune system	HLA-DR B1*1202, HLA-B*4601, HLA-B*0703 and HLA-Cw*0801	Increased susceptibility to severe SARS-CoV-1 infection	Keicho et al.2009 [126] Chen et al. 2006 [127]
			HLA-A*0201, HLA-Cw1502 and HLA-DR0301	Correlated with protection against SARS-CoV-1 infection	Wang et al. 2011 [128]
			HLA-DQB1*02:0 and HLA-DRB1*11:01	Higher risk of MERS-CoV infection	Hajeer et al. 2016 [129]
AHSG	3q27.3	Involved in brain development, formation of bone tissue, and endocytosis	rs2248690, risk allele, T	Might affect SARS-CoV-1 infection outcome	Zhu et al. 2011 [137]
CCL5	17q12	Active role in leukocyte recruitment	rs2280788, risk allele, C; rs4239252, risk allele, A	Might affect SARS-CoV-1 infection outcome	Ng et al. 2007 [83]
ICAM3	19p13.2	Initiation of the immune response, potent signaling molecule, and adhesion molecule	rs2304237, risk allele, C; rs3181049, risk allele, A; rs3176767, risk allele, G; rs4611572, risk allele, G; rs2304240, risk allele, G	Might affect SARS-CoV-1 infection outcome	Chan et al. 2007 [139]
IL4	5q31.1	Induces differentiation of Th0 cells to Th2 cells	rs2070874, risk allele, T	Might affect SARS-CoV-1 infection outcome	Patarčić et al. 2015 [75]
IFN-γ	12q15	Critical cytokine for innate and adaptive immunity against viral infection	rs2430561, risk allele, A	Risk factor for SARS susceptibility	Chong et al. 2006 [69]
Other genes					
DBP	4q11–q13	Regulator of total and free vitamin D metabolite levels	G allele at rs7041	Increases the risk of HCV infection	Xie et al. 2018 [143]
VDR	12q13.11	Bone homeostasis, skin biology, immune system, oral health	rs2228570, risk allele, T	Reported as a risk factor for infection with enveloped viruses, including RSV infection	Laplana et al. 2018 [153]
CD147	19p13.3	Role in intercellular recognition	rs2283574, rs6757, rs8637, rs4919862, rs6758, rs8259, rs4919859 and rs28915400	Related to multiple diseases and disorders	Jin et al. 2020 [175] Zhou et al. 2014 [176]

Table 2 Human genetic polymorphisms related to the outcome of infection with SARS-CoV-2

Gene	Location	Functions	Polymorphisms	Outcomes	References
Viral attachment and entry					
ACE2	Xp22.2	a) Converts angiotensin I to angiotensin 1-9	rs2285666,	Decreased infection and fatality rate	Srivastava et al. 2020 [45]
			rs4646116, rs267606406, rs143936283	Increased susceptibility	Wang et al. 2020 [46]
		b) Converts angiotensin II to angiotensin 1-7	rs961360700, rs146676783, rs1244687367	Decreased susceptibility	Wang et al. 2020 [46]
TMPRSS2	21q22.3	Transmembrane serine protease that increases virus entry	rs2070788, rs9974589, rs7364083	Increased susceptibility	Asselta et al. 2020 [15]
			rs77675406, rs713400, rs112657409, rs11910678	Increased susceptibility	Senapati et al. 2020 [62]
			rs2070788, rs383510, rs464397, rs469390	Increased susceptibility	Irham et al. 2020 [63]
Immune responses					
TLR3	4q35.1	Sensor of double-stranded RNA	rs73873710	Improved recognition of SARS-CoV-2 dsRNA	Teimouri et al. 2020 [140]
			rs3775290, rs3775291	Decreased recognition ofSARS-CoV-2 dsRNA	
IFIH1	2q24.2	Intracellular sensor of viral RNA	rs1990760	Decreased susceptibility to SARS-CoV-2 infection (T allele)	Maiti. 2020 [118]
CCR5	3p21.31	Chemokine receptor	CCR5 Δ32	Increased susceptibility to SARS-CoV-2 infection and mortality	Panda. 2020 [74]
IFNL4	19q13.2	Immune response to viral infection	rs368234815TT/ΔG	Higher viral loads	Amodio et al. 2020 [79]
Other genes					
DBP	4q11–q13	Regulator of total and free vitamin D metabolite levels	rs7041	GT and TT genotype are positively and negatively related to the rate of SARS-CoV-2 infection and mortality, respectively	Karcioglu et al. 2020 [141]
DPP4	2q24.2.	Serine exopeptidase	rs13015258	Expression of key regulatory genes related to internalization of SARS-CoV-2 into the cell	Senapati et al. 2020 [62]
VKORC1	16p11.2	Decreased vitamin K level	1639A (rs9923231)	Associated with protection against thrombotic complications of COVID-19	Janssen et al. 2020 [217]

affected by androgen and estrogen hormones, which might partially explain the observed gender differences in disease severity [53, 57, 61]. A study in Italy demonstrated that some SNPs, including rs2070788, rs9974589, and rs7364083, were associated with a higher expression level of TMPRSS2 and played a considerable role in determining the severity of COVID-19 [15]. Moreover, four other polymorphisms – rs77675406, rs713400, rs112657409, and rs11910678 of TMPRSS2 – affect the expression of the TMPRSS2 gene [62]. Another study showed that four

variants of TMPRSS2 – rs2070788, rs383510, rs464397 and rs469390 – which affect the expression of TMPRSS2 in lung tissue, had a higher frequency in European and American populations than in Asian populations. These observations might explain the relatively higher susceptibility of European and American populations to SARS-CoV-2 infection [63] (Table 1). Furthermore, a recent report by Fuentes et al. demonstrated that synonymous variants of rs61735794 and rs61735792 were significantly associated with SARS-CoV-2 infection outcome [64].

Variations in the TMPRSS2 gene have also been associated with the outcome of other viral infections. For instance, Cheng et al. reported that rs2070788 and rs383510 polymorphisms were associated with higher susceptibility to H1N1 and H7N9 infection. Based on these findings, the authors suggest that people carrying these polymorphisms might have a higher risk of progression to severe disease [65].

Immune system gene polymorphism

The relationships between polymorphisms of the immune genes and the outcome of viral infections have always been a matter of concern. Considering the pivotal role of these genes in viral clearance and immunopathogenesis, polymorphisms in these regions are likely to affect the outcome of an uncharacterized disease like COVID-19 (Tables 1, 2).

Cytokines

Cytokines are small proteins (~5–20 kDa) that are important for cell signaling and include interleukins, chemokines, lymphokines, interferons, and tumour necrosis factors. In severe cases of SARS-CoV-2 infection, high concentrations of innate inflammatory cytokines, including type I interferons (IFNs), tumor necrosis factor α (TNF-α), IL-6, IL-1β, and some chemokines, including CCL-2, CCL-3, CCL-5, and IP-10, are secreted by epithelial and immune cells [66]. This uncontrolled and excessive release of pro-inflammatory cytokines, i.e., cytokine storm, has been observed in patients infected with influenza virus, SARS-CoV, and MERS-CoV [66, 67]. A cytokine storm is characterized by a strong proliferation and hyperactivation of T lymphocytes, overexpression of more than 100 pro-inflammatory genes, and massive endothelial and epithelial cell apoptosis of the lung, which results in alveolar edema, hypoxia and ARDS, and finally, death [66, 68]. The significant role of this aberrant immune response in severe COVID-19 has inspired the search for antibodies that block pro-inflammatory cytokines such as IL-6 and IL-17 as well as monocyte recruitment elements [68]. Additional immune gene variations have been associated with susceptibility to SARS-related pathogenesis. For instance, the IFN-γ +874A allele variant is considered a risk factor for susceptibility to SARS [69]. Interleukin-6 (IL-6, a 21-kDa) glycoprotein polymorphism has been associated with viral infections such as influenza virus, RSV, hepatitis B virus (HBV), and HCV [70]. For example, the IL6-174 C/C genotype (rs1800795) is associated with severe RSV infection [71]. Although IL-6 plays a significant role in the initiation of the cytokine storm in SARS-CoV-2-infected patients, little information is available concerning IL-6 polymorphisms and the pathogenesis of idiopathic pulmonary fibrosis in SARS-CoV-2 infection. A meta-analysis showed that the IL6 174C allele is associated with elevated cytokine production and the outcome of pneumonia [72]. Based on the regulatory function of IL-6 for CD4 T cell fate, it can be hypothesized that studying polymorphisms of the IL-6 genes may provide further insights into COVID-19 pathogenesis [73]. In fact, IL6 polymorphism is considered a valid indicator for the severity or pathology associated with SARS-CoV-2 infection. Moreover, Panda et al. reported that the CCR5 Δ32 polymorphism might influence susceptibility to SARS-CoV-2 infection [74]. Also, IL4 gene polymorphism (SNP: rs2070874; risk allele: T) might influence the outcome of SARS-CoV-1 infection [75].

The IFNAR2 gene is located on chromosome 21q22.11 and encodes the IFN-α/β receptor beta chain [76]. Data analysis has shown that polymorphism at the rs2236757 locus of the IFNAR2 gene is associated with the outcome of COVID-19 disease [77].

IFNL4 is another gene that might be involved in SARS-CoV-2 infection. IFNL4 is located on chromosome 19q13.2 and is involved in the defense against viral infections, such as HCV, RSV and influenza virus [78]. Amodio et al. reported that polymorphisms at the rs368234815TT/ΔG locus of the IFNL4 gene are associated with a higher SARS-CoV-2 viral load [79].

Chemokine (C-C motif) ligand 5 (CCL5), also known as regulated on activation, normal T cell expressed and secreted (RANTES), is a protein involved in inflammatory and immunoregulatory processes and encoded by the CCL5 gene located on chromosome 17q12 [80–82]. CCL5 gene polymorphism (SNP rs2280788, risk allele, C; SNP rs4239252, risk allele, A), is associated with SARS-CoV-1 infection outcome [83, 86].

2′-5′-oligoadenylate synthetase and interferon-induced GTP-binding protein Mx1

The 2′-5′-oligoadenylate synthetase (OAS) family includes IFN-inducible genes that have a prominent role in innate immunity against viral infections such as picornaviruses. This family include four types of IFN-inducible genes: OAS1, OAS2, OAS3, and OAS-like protein [84]. OAS interferes with viral replication through the induction of apoptosis and inhibition of protein synthesis [84].

The OAS–RNase L axis is rapidly activated following cellular infection with various RNA viruses, e.g., flaviviruses, alphaviruses, picornaviruses, and coronaviruses [85, 87]. Moreover, the variant of rs10735079 in a gene cluster encoding antiviral restriction enzyme activators (OAS1, OAS2, OAS3) is associated with SARS-CoV-2 infection outcome [77]. Human Mx1 is another IFN-type-1-induced gene that is located on chromosome 21q22.3, and the encoded protein targets viral nucleoproteins [88, 89]. Regarding the role of these genes in innate immunity against viral infections, some studies have suggested that SNPs in the OAS1 gene and MxA promoter might be associated with a higher susceptibility to more-severe SARS infection [90]. In this regard, He et al. reported that SNPs in the 3'-UTR region of the OAS1 gene and the MxA promoter were associated with susceptibility to SARS in the Han population of China [90]. The results of their study revealed that the frequency of the AG and GG genotypes of the OAS1 gene was higher in the control group than in SARS patients. Therefore, they suggested that the G allele might have a protective effect against SARS-CoV infection [90]. Also, studies have revealed that polymorphisms at the -123 (C/A) and -88 (G7T) loci of the Mx1 gene affect the levels of protein expression, thereby influencing disease outcomes in patients infected with HBV, HCV, and enterovirus 71, and SARS-CoV [90–98].

CD14

CD14 is a transmembrane glycoprotein that is located on chromosome 5q31.3 and expressed on cells of the monocyte-macrophage lineage and neutrophils [99]. CD14 is involved in a variety of biological activities, including cell differentiation and host-pathogen interactions, and it is a key molecule in the activation of innate immune cells [99]. It has been reported that the frequency of CD14-159CC polymorphism (rs2569190) is significantly higher among patients suffering from severe SARS, indicating its importance in determining the disease outcome [99]. On the other hand, it has also been reported that IL-10 and TNF-α polymorphisms are not associated with SARS sensitivity [69]. In a study carried out by Tu et al., it was found that the CCL2G-2518A (rs1024611) polymorphism and variations in codon 54 in MBL (rs1800450) are significantly associated with the risk of SARS-CoV infection [100].

CD209

The CD209 gene is located on chromosome 19p13.2 and encodes a critical dendritic-cell surface receptor named dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) [101, 102]. In innate immunity and antiviral defense, DC-SIGN has key functions, including DC migration, antigen uptake, and T-cell priming [103]. DC-SIGN was first discovered as an attachment factor for HIV that binds to the viral envelope glycoprotein and increases the efficiency of infection [104]. Subsequently, DC-SIGN and DC-SIGNR (or L-SIGN) were shown to enhance Ebola virus and SARS-CoV infection [105]. Studies have suggested that polymorphisms in the DC-SIGN gene might be involved in susceptibility/resistance to dengue virus, tick-borne encephalitis virus, cytomegalovirus, and SARS-CoV-2 infection [106, 107, 110]. Supporting this hypothesis, Iyer et al. recently reported that polymorphisms at rs2287886 and rs8105483 are correlated with protection, and those at rs11881682, rs8105572, rs7252229, rs11465384, rs7248637, and rs1146541 are correlated with risk of/susceptibility to symptomatic COVID-19 disease [106] (Table 2). In addition, they revealed that the G allele in rs10518270 and rs2335525 SNPs is a risk allele in SARS-CoV-1 infection [106].

Mucin 5B

The mucin 5B (MUC5B) gene is located on chromosome 11p15.5 and encodes MUC5B, which plays a role in the viscoelastic and lubricating properties of the mucosa [108]. The MUC5B gene is upregulated in some human diseases related to pulmonary fibrosis and end-stage lung disease [109]. Many symptoms related to MUC5B upregulation in lung disease resemble COVID-19 disease [106]. It has been suggested that the SNPs in the MUC5B gene might be associated with human diseases such as pulmonary fibrosis and COVID-19 disease [106, 110–112]. Iyer et al. reported that polymorphisms at rs2672794, rs56235854, rs7115457, rs2735727, rs12417955, and rs56367042 might be associated with susceptibility to COVID-19 disease and that those at rs2735733, rs2249073, rs2857476 might be associated with comorbidities [106].

IFN-induced transmembrane protein 3

Another IFN-inducible gene is the IFN-induced transmembrane protein 3 (IFITM3) gene, which is located on chromosome 11p15.5 [113]. This gene encodes a membrane protein that inhibits viral fusion with cholesterol-depleted endosomes [113]. It has been shown that IFITM3 is active against viral infections, including influenza virus, SARS-CoV, dengue virus, Ebola virus, and HIV-1 [114, 115]. Functional polymorphisms in this gene have been studied in several infections. Iyer et al. reported that polymorphisms at rs34481144 might have a protective role, whereas those at rs7948108, rs12252, rs4804800, rs4804803, rs6598045, and rs3888188 might increase susceptibility to SARS-CoV-2 infection [106]. Furthermore, Gómez et al. revealed that the rs12252 C variant of the IFITM3 gene might be associated with COVID-19 disease outcome [116].

IFN induced with helicase C domain 1

The IFN induced with helicase C domain 1 (IFIH1) gene is located on chromosome 2q24.2, is induced by IFN type I, and encodes MDA5, an intracellular sensor of viral RNA [117]. It has been reported that the lower frequency of the T allele at the locus rs1990760 of IFIH1 in the African-American population might be associated with COVID-19 infection outcome due to decreased expression of IFN-β [118]. Formyl peptide receptor 1 (FPR1), a pattern-recognition receptor, is involved in the induction of innate immune responses against bacterial infections [119]. Although it has been reported recently that FPR1 expression is involved in lung inflammation and fibrosis, a genetic investigation showed no association between polymorphisms at the rs867228 and rs5030880 loci of the FPR1 gene and the severity of COVID-19 disease [120] (Table 2).

Dipeptidyl peptidase 9

Dipeptidyl peptidase 9 (DPP9) is a Dipeptidyl peptidase 9 (DPP9) is a member of the S9B family, and its gene is located on chromosome 19p13.3 [77]. DPP9 is a serine protease that plays an important role in antigen presentation, activation of inflammasomes, and cleavage of important elements of the immune system such as chemokines (CXCL10, CXCL11, and CXCL12) [121–123]. It has been reported that polymorphisms at the locus rs2109069 of the DPP gene might be associated with COVID-19 outcome. For instance, variations at this location were associated with idiopathic pulmonary fibrosis in COVID-19 patients [77, 124].

Tyrosine kinase 2

Tyrosine kinase 2 (Tyk2), a member of the Janus kinase (JAK) family, is associated with the cytoplasmic domain of type I and II cytokine receptors [77]. The Tyk2 gene is located on chromosome 19p13.2. It has been reported that polymorphisms at rs2109069 near the Tyk2 gene might be associated with COVID-19 outcome [77].

Human leukocyte antigen

Human leukocyte antigens (HLAs) are encoded by the major histocompatibility complex (MHC) genes in humans and are responsible for regulation of the immune system. The HLA gene complex is located on chromosome 6p21 [125]. Previous investigations have shown that various polymorphisms of HLA, such as HLA-DR B1*1202, HLA-B*4601, HLA-B*0703, and HLA-Cw*0801 might predispose carriers to more-severe SARS-CoV infection [126, 127]. In contrast, the HLA-A*0201, HLA-Cw1502, and HLA-DR0301 alleles are correlated with protection from SARS-CoV infection [128], while HLA-DQB1*02:0 and HLA-DRB1*11:01 are associated with a higher risk of MERS-CoV infection [129]. Amoroso et al. reported that HLA-DRB1*08 was more frequent in COVID-19 patients and correlated with an increased mortality rate [130].

Other immune system genes

Alpha-2-HS-glycoprotein (AHSG, alpha-2-Heremans-Schmid glycoprotein or fetuin-A) is a protein that is encoded on chromosome 3q27.3 [131]. This protein is synthesized by hepatocytes and adipocytes and has several functions in brain development, endocytosis, and the formation of bone tissue [132]. Like carrier proteins (e.g., albumin) it is present in the serum, and SNPs have been associated with serum fetuin-A levels [133]. Fetuin-A can increase insulin resistance and inflammation, and it is essential for the deactivation of macrophages by modulating endogenous cations [134]. Low serum levels of AHSG have been associated with uncontrolled production of proinflammatory cytokines [135, 136]. Furthermore, polymorphisms in the AHSG (SNP rs2248690; risk allele, T) gene might affect the outcome of SARS-CoV-1 infection [137]. So far, polymorphisms in this gene have not been studied in COVID-19 patients.

The intercellular adhesion molecule 3 (ICAM3) gene is located on chromosome 19p13.2. ICAM3 acts as an adhesion molecule and a signaling molecule, and it also functions in the initiation of the immune response [138]. ICAM3 gene polymorphisms (SNP rs2304237, risk allele, C; SNP rs3181049, risk allele, A; SNP rs3176767, risk allele, G; SNP rs4611572, risk allele, G; SNP rs2304240, risk allele, G) might affect SARS-CoV-1 infection outcome [139].

The Toll-like receptor 3 (TLR3) gene is located on chromosome 4q35.1. TLR3 is a member of the TLR family of pattern recognition receptors and has an important function in sensing and activation of the innate immune system. An *in silico* analysis by Teimouri et al. showed that polymorphisms at rs3775290 and rs3775291 enhanced recognition of SARS-CoV-2 dsRNA by TLR3, whereas those at rs73873710 decreased its efficiency [140].

Other gene polymorphisms related to SARS-CoV-2 infection

Vitamin D binding protein

Vitamin D binding protein (DBP) is a multifunctional protein that is involved in various clinical conditions by

regulating vitamin D metabolite levels [141]. The DBP gene is located on chromosome 4q11–q13 and is predominantly expressed in liver tissue [142]. Some factors such as estrogen, glucocorticoid, and inflammatory cytokines modulate DBP expression levels. Consisting of 458 amino acids, DBP has been identified as the most polymorphic protein [142]. Allele variations have a substantial impact on its biological functions (e.g., the alleles Gc1s (rs7041 locus) and Gc2 (rs4588 locus) increase the affinity of DBP for vitamin D and are associated with lower free vitamin D levels [141]. In HCV infection, the G allele at the rs7041 locus has been reported to be associated with the expression of a high-affinity receptor, which increases the risk of infection [143]. People carrying the GG genotype at the rs4588 locus of the Gc2 polymorphic region have lower levels of 25(OH) D compared to individuals carrying the AA genotype following vitamin D supplementation [144]. Batur et al. showed that DBP variations such as the GT genotype at rs7041 are significantly correlated with a higher frequency of COVID-19-related deaths, while the TT genotype showed a significant negative correlation with mortality [141]. In addition, the polymorphism at the rs4588 locus had no significant impact on COVID-19 severity [141]. These findings indicate that variations in mortality rate may be explained by DBP polymorphisms, which affect vitamin D metabolism [141].

Vitamin D receptor

The vitamin D receptor (VDR) gene is located in the region q13.11 of chromosome 12 [145]. VDR is a nuclear receptor that functions as a transcription factor when activated by its ligand [146]. Most of the VDR activity is controlled by the interaction with the ligand 1,25(OH)2D, but some functions are vitamin-D-independent. [147, 148]. VDR belongs to the steroid receptor family, which includes retinoic acid, thyroid hormone, sex hormones, and adrenal steroid receptors, which have a broad distribution among different cells [149, 150]. Vitamin D signaling is involved in calcium and bone homeostasis, skin biology, immune health, oral health, cancers, and cardiovascular diseases [148]. Many cells of the innate and adaptive immune system express VDR. Some of these cells express CYP27B1 for producing the biologically active form of vitamin D [148]. Data from experiments using animal models have demonstrated that vitamin D/VDR signaling modulates autoimmune T cell responses and immune-inflammatory reactions, but the physiological activity in humans is not completely understood [151]. Therefore, its role in the pathogenesis and outcome of immune-inflammatory diseases remains to be elucidated [148, 152].

Based on a meta-analysis by Laplana et al., a polymorphism at locus rs2228570 was associated with viral infections. The TT genotype and T allele were reported to be risk factors for infections with enveloped viruses, including RSV [153]. There are numerous findings indicating that vitamin D supplementation can reduce the risk of severe infection and death related to influenza and COVID-19. However, none of the studies have reported the importance of vitamin D receptor polymorphisms in COVID-19 disease outcome [154]. When examining the antimicrobial role of vitamin D in different populations, we need to take VDR polymorphisms into account.

Glucose-regulated protein 78 kDa

Glucose-regulated protein (GRP78), or heat shock protein family A (HSPA) member 5, belongs to the HSP70 family and is found on the membrane of the endoplasmic reticulum (ER). The gene encoding this protein is located on chromosome 9q33.3 [155, 156]. GRP78 plays an accessory role in many stages of the viral life cycle, including viral attachment and entry (facilitating or alternative factor), protein production (proper folding and processing), release (assembly and maturation), and re-infectivity (released together with mature virions and acting as accessory infectivity factor) [157]. Bioinformatic modeling has predicted favorable binding between GRP78 and the III (C391-C525) and IV (C480-C488) regions of the SARS-CoV-2 S protein [158]. In cells harboring the -415A/-180G allele, expression of HSPA5 was significantly increased compared to cells harboring the -415 G/-180 del allele following ER stress [159]. GRP78 expression and its polymorphisms may be associated with SARS-CoV-2 infection and mortality rates, but their role in COVID-19 is still poorly understood.

CD147 polymorphisms

CD147 is a cell-surface glycoprotein belonging to the immunoglobulin superfamily that plays a role in intercellular recognition [160]. The CD147 gene encompasses a stretch of 7500 bp on chromosome 19p13.3 and encodes a protein from eight exons [161, 162]. CD147 is also known as extracellular matrix metalloproteinase inducer (EMMPRIN) or basigin and is expressed by a variety of cell types, including endothelial cells, epithelial cells, and lymphocytes [163–166]. It has been reported that CD147 regulates proliferation, differentiation, migration, metastasis, and apoptosis of tumor cells, particularly in hypoxic situations [167, 168]. Therefore, the role of CDl47 in the progression and metastasis of tumors has been studied [169].

CD147 has recently been identified as a marker of inflammation [170]. Moreover, some studies have shown that CD147 is an important molecule in proteolysis and inflammation [171]. CD147 has various ligands, e.g., integrins, cyclophilin, and *Plasmodium falciparum* reticulocyte

binding-like homologue 5 [168]. The role of CD147 in infections by viruses such as Kaposi's sarcoma-associated herpesvirus (KSHV), HBV, HCV, and HIV has been studied extensively, and these studies have supported the importance of CD147 in viral pathogenesis and tumorigenesis [168]. Interactions of CD147 with cyclophilin A during HIV infection accelerate its uptake into cells. A similar mechanism has been reported for SARS coronavirus infection [172, 173]. Furthermore, CD147 on epithelial cells acts as a receptor for measles virus [174]. Studies have reported that the CD147 gene contains a number of SNPs in coding and regulatory regions, including rs2283574, rs6757, rs8637, rs4919862, rs6758, rs8259, rs4919859, and rs28915400. These regions might be involved in numerous diseases and disorders [175, 176]. For instance, it has been reported that polymorphisms in the CD147 gene might effectively contribute to the initiation and progression of acute coronary syndrome and skin diseases [171, 177, 178]. Although CD147 has been studied in the context of viral pathogenesis and tumorigenesis, the significance of its polymorphisms in viral infection outcome remains to be determined [168].

Recent studies have suggested that CD147 can serve as an alternative receptor for SARS-CoV-2 [179]. Although some studies have investigated ACE-2 polymorphisms that enhance or diminish binding of the S protein to ACE-2, polymorphisms that affect S protein binding to CD147 have not been reported in SARS-CoV-2 infection. Meanwhile, Wu et al. have reported that the polymorphism T/A (rs8259) in the 3′-UTR of the CD147 gene, which interacts with miR-492, alters the expression of CD147 [178]. However, no studies have been conducted to investigate the relationship between SNPs of CD147 or miRNA-492 and the risk of SARS-CoV-2 infection. miRNA-492 *is encoded* on chromosome 12q22 and binds to complementary sequences in the 3′-UTRs of target mRNAs.

Dipeptidyl peptidase 4 (DPP4)

Dipeptidyl peptidase 4 (DPP4), also known as CD26, is encoded by the DPP4 gene, which is located on chromosome 2q24.2 [180]. DPP4 is a serine exopeptidase that is expressed on the surface of most cell types and cleaves X-alanine or X-proline dipeptides from the N-termini of polypeptides. DPP4 has been identified as the cellular entry receptor for MERS-CoV. Current data suggest that CD26 does not act as a receptor for SARS-COV-2 [181]. However, one study has shown that polymorphisms in the rs13015258 locus in the CD26 gene affect the expression of key regulatory genes related to internalization of SARS-CoV-2 into the host cell [62].

Neuropilin 1

Understanding the mechanisms and pathways involved in the cellular entry of SARS-CoV-2 is essential to delineate virus tropism to develop preventive strategies. In addition to ACE-2 and CD147, receptor for advanced glycation end-products (RAGE), and olfactory receptors, recent experiments have suggested neuropilin 1 (NRP-1) to be a new mediator of SARS-CoV-2 entry in the nervous system [181, 182]. An *in vitro* study confirmed the direct binding of the S1 CendR motif of SARS-CoV-2 NRP-1 [181]. Moreover, it has been shown that NRP-1 binds to furin-cleaved substrates and consequently enhances the infectivity of SARS-CoV-2. This mechanism can be targeted by NRP-1 monoclonal antibodies to block entry of the cell by the virus [182].

NRP-1 is a type I transmembrane protein, and its gene is located on chromosome 10p11.22 [153]. NRP-1 is involved in providing cues for axonal guidance and neuronal development. Furthermore, it has been identified as a co-receptor for multiple ligands, such as vascular endothelial growth factor (VEGF), semaphorins (SEMA), and transforming growth factor beta (TGF-β) [184, 185]. A higher level of expression of NRP-1 has been detected in the upper respiratory tract and olfactory epithelium covering the nasal cavity [186]. Similar polybasic furin-type cleavage sites (RRAR^S) in the S1–S2 junction of the spike glycoproteins have been observed in other human viruses including Ebola virus, HIV-1, and highly virulent strains of avian influenza virus. In contrast, a similar site was found to be lacking in SARS-CoV-1 [187, 188].

There are a growing number of studies investigating the role of NRP-1 in the immune response. Hwang et al. demonstrated that NRP-1 regulates the secondary CD8 T cell response to viral infections. NRP-1 was also found to be important for the function of regulatory T (Treg) cells [189]. Overexpression of NRP-1 in T-reg cells enhances their interactions with dendritic cells, which attenuated the immune responses in the absence of danger signals. Based on these findings, polymorphisms in the NRP-1 gene might affect the immune response to SARS-CoV-2 infection by inhibiting antigen presentation in the lymph nodes and subsequent viral clearance. In one study, 11 functional SNPs were reported in the NRP-1 gene, which have been associated with various clinical conditions. For instance, a polymorphism at rs2228638 was shown to be associated with an increased risk of cyanotic congenital heart disease [190]. Recently, it was reported that binding of miR-338 to the 3'-UTR of NRP-1 significantly inhibits the expression of NRP-1. Since the rs10080 SNP is located in the 3'-UTR region, it might affect the expression pattern of NRP-1 [190]. For instance, it has been reported that the G allele of rs10080 can downregulate the expression of NRP-1 [191]. Therefore, individuals carrying the G allele might express lower levels of NRP-1 on

the target cells, which alters the neuropathogenesis associated with COVID-19 disease. More investigations regarding the effect of SNPs in NRP-1 on the pathogenesis of SARS-CoV-2 infection in other tissues are recommended.

Heme oxygenase 1

Heme oxygenase 1 (HO-1, HMOX1) is located on chromosome 22q12.3 [191]. The heme oxygenase system is an anti-inflammatory cytoprotecting system that includes HO-1 and HO-2. It degrades heme to bilirubin, free iron, and carbon monoxide and plays an important role in the antioxidant and antiapoptotic activity of the cells [192]. The high-affinity binding of the SARS-CoV-2 spike protein to porphyrin [193] upregulates the formation of reactive oxygen species (ROS) and free heme and decreases the level of HO-1 [192, 194, 195]. Therefore, the SARS-CoV-2-porphyrin complex may cause impairment of HO-1 signaling by downregulating HO-1 gene expression, which results in severe oxidative stress induced by free heme and iron [192, 194, 196]. It has been reported that a genetic polymorphism, a di-nucleotide repeat of GT, in the promoter region of the HO-1 affects the transcription of HO-1 and might be associated with the COVID-19-induced cytokine storm [192, 197–202]. In this regard, Fakhouri et al. concluded that individuals with longer GT repeats in the HO-1 promoter were at higher risk of developing severe COVID-19 disease [192]. Moreover, it has been reported that the T allele at the locus rs2071746 of the HO-1 gene can modulate the expression of HO-1 and influence the severity of COVID-19 disease [203].

Apolipoprotein L1

Apolipoprotein L1 (APOL1), a member of APOL gene family, is encoded by a gene located on chromosome 22q12.3 [204]. APOLs play important roles in lipid transport and metabolism, innate immunity, apoptosis, and autophagy [205–211]. Furthermore, APOL1 is involved in inflammatory and pro-inflammatory responses. For instance, cytokines such as TNF-α and IFN-γ can upregulate APOL1 expression [210]. Recently, the relationship between COVID-19 disease and APOL1 polymorphism in African patients was reported [212]. These researchers emphasized the potential key role of G1 and G2 alleles in the formation of collapsed focal segmental glomerulosclerosis (FSGS) related to SARS-CoV-2 [212]. Moreover, Larsen et al. reported that CG variants of the APOL1 gene were associated with COVID-19-related severity of kidney disease [213]. The CG genotype has not been reported in Chinese and European populations. Therefore, the high-risk APOL1 genotypes might exist only in African populations [213, 214].

Vitamin K epoxide reductase complex subunit 1

The vitamin K epoxide reductase complex 1 (VKORC1) gene is located on chromosome 16p11.2 [215]. Polymorphism at the regulatory -1639A locus of the VKORC1 gene is common in the East Asian population and is associated with low vitamin K turnover [216]. Based on reported data, it has been proposed that VKORC1-1639A polymorphisms (rs9923231) are associated with protection against thrombotic complications of COVID-19 infection, which might partially explain the differences in the severity of COVID-19 infection between Western and Eastern countries [217].

ABO blood group system

The ABO blood group system is based on the presence or absence of A and B glycan antigens on red blood cells. A particular ABO blood type might confer resistance to infectious diseases. Several studies found an association between the ABO blood group and susceptibility to SARS-CoV-2 infection. For instance, individuals with blood group O had a lower risk of infection than those with blood group A [130, 218]. Moreover, SNP rs657152 at the locus 9q34.2, which mapped on the ABO locus, was reported to be a genetic susceptibility locus in COVID-19 patients diagnosed with respiratory failure [219].

Conclusion

In addition to being a local respiratory disease, COVID-19 is a complex multi-organ disease in which human genetic polymorphisms play a distinctive role in the disease outcome. Currently, there is insufficient and controversial knowledge about the role of gene polymorphisms in the pathogenesis of SARS-CoV-2 infection. In this review, we have provided a comprehensive overview of the relevant research data currently available. The affinity-determining variants in the ACE-2 gene, such as rs2285666, rs4646116, rs267606406, rs143936283, rs961360700, rs146676783, and rs1244687367, are associated with SARS-CoV-2 infection outcome. The expression level of TMPRSS2 plays a considerable role in determining the severity of COVID-19. Polymorphisms in the TMPRSS2 gene, including rs2070788, rs9974589, and rs7364083, are associated with increased expression of this gene. The G allele at rs10080 of the NRP-1 gene might be associated with lower expression of the NRP-1 protein on target cells and might result in decreased COVID-19 pathogenesis. Moreover, polymorphisms in the immune-related genes, including TLR3, IFNL4, IFIH1, and CCR5, are likely to influence the outcome of COVID-19 disease. Finally, genetic polymorphisms in some other genes,

including the HO-1, APOL1, VKORC1, DPP4, and DBP genes, might influence the SARS-CoV-2 infection outcome. The present review was an attempt to clarify the importance of human gene polymorphisms in the clinical outcome of SARS-CoV-2 infection. This overview provides insights for disease management and control.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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