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Human Genetic Polymorphisms Associated with Susceptibility to COVID-19 Infection and Response to Treatment

Necla Benlier, Nevhiz Gundogdu and Mehtap Ozkur

Abstract

Clinicians and researchers observing the natural history of endemic and epidemic infections have always been fascinated by the vagaries of these diseases, in terms of both the changing nature of the disease severity and phenotype over time and the variable susceptibility of hosts within exposed populations. SARS-CoV-2, the virus that causes COVID-19 and is believed to originate from bats, quickly transformed into a global pandemic. The pandemic of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been posing great threats to the global health in many aspects. Currently, there are no proven effective vaccines or therapeutic agents against the virus. Comprehensive understanding of the biology of SARS-CoV-2 and its interaction with hosts is fundamentally important in the fight against SARS-CoV-2. Advanced age, male sex, and comorbidities such as hypertension and cardiovascular disease as well as diabetes and obesity have been identified as risk factors for more severe COVID-19. However, which and to what extent specific genetic factors may account for the predisposition of individuals to develop severe disease or to contract the infection remains elusive. The increasing availability of data from COVID-19 patient populations is allowing for potential associations to be established between specific gene loci and disease severity, susceptibility to infection, and response to current/future drugs.

Keywords: Human Genetic Polymorphisms, SARS-COV-2, COVID-19, Genetic Susceptibility

1. Introduction

Variability in response to drugs, both in terms of efficacy and tolerability, and ways to customize treatments according to their characteristics have become important topics of medical research. It was determined that genetic variations in some ethnic groups may affect the response to drug and the outcomes of treatment [1]. Various enzymes are often involved in drug absorption/distribution/metabolism/excretion (ADME) processes and show multiple interactions [2].

Gene polymorphisms are sequence variations at specific locations within the genome and are observed in more than 1% of the population. Genetic polymorphisms can alter the coding of proteins or their expression, and affect natural

or acquired immunity [3]. Single nucleotide polymorphisms (SNPs) have been studied in relation to various diseases, which are associated with variations of DNA sequence with phenotypic changes [4]. Variations in the genes control competence in the cellular and humoral immune systems, which define the individual risk level for diseases [5, 6].

2. SARS-CoV-2

After the investigation that started with the World Health Organization (WHO) China Country Office reporting a cluster of pneumonia cases of unknown cause in Wuhan city of Hubei province of China on 31 December 2019, it was identified on January 7, 2020 that the agent was a new coronavirus that causes infection in humans. The causative virus was designated as 2019-nCoV (2019-novel coronavirus) by the WHO and SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2) by the International Virus Taxonomy Committee, and the disease caused by the virus was named as COVID-19 (coronavirus disease- 2019) [7, 8].

The disease is highly contagious and its main clinical symptoms are fever, dry cough, fatigue, muscle pain and shortness of breath. Since the first reported case of COVID-19 in the city of Wuhan, China, at the end of 2019, COVID-19 has rapidly spread all over China and then to all countries of the world [9]. It was confirmed that the virus spreads from person to person, through close contact and via respiratory particles that are generated by coughing or sneezing [10]. Most of the studies conducted in Wuhan at the beginning of the epidemic showed that the first patients worked in or visited a seafood market in Wuhan. Initially, it was thought to be caused by snakes, but later studies have shown it to be related to bats. As the pandemic progressed, it was shown that this viral infection is transmitted from one person to another through droplets and by touching the face with hands exposed to contaminated surfaces [11]. The virus can be found in respiratory secretions of patients 1–2 days before the onset of clinical symptoms and two weeks after disease symptoms [12].

Coronaviruses belong to the subfamily *Coronavirinae* of the family *Coronaviridae* and include four genera: Alphacoronavirus, Betacoronavirus, Gammacoronavirus and Deltacoronavirus. The genome of CoVs (27–32 kb) is a single-stranded positive-sense RNA (+ ssRNA) that is larger than other RNA viruses [13]. The genome size of SARS-CoV-2 is approximately 29.9 kb [14].

Coronaviruses contain four structural proteins, namely S (Spike) protein, E (Envelope) protein, M (Membrane) protein and N (Nucleocapsid) protein, which are involved in the formation of mature virus particles (virions) and the emergence of infection [15]. The S protein is responsible for the formation of spikes on the surface of the coronavirus, and these protrusions play a key role in the attachment of the virus to host cell receptors and its entry into the cell. The spike protein is also the main antigenic component of the virus [16].

Depending on viral strains and cell types, coronavirus S proteins can be cleaved by one or more host proteases, including cathepsins, furin, neutrophil elastase (ELANE), transmembrane protease serine protease-2 (TMPRSS-2), and possibly TMPRSS11A [17–19]. The presence of these proteases on target cells largely determines whether coronavirus particles enter cells via the plasma membrane or endocytosis. Hoffmann et al. showed that SARS-CoV-2 uses transmembrane protease 2 (TMPRSS2) for S protein priming and the SARS-CoV receptor angiotensin-converting enzyme 2 (ACE2) for entry into target cells [20]. Likewise, Ou et al. found that cathepsin L (CTSL) is essential to the virus entry in the host cell [21]. Moreover, it was reported that the S protein of the A2a subtype possesses an additional elastase-specific proteolytic cleavage site that enhances the virus's ability

to penetrate host cells [19]. This virus subtype has been reported in China and has spread rapidly in North America and Europe [22, 23].

Coronaviruses contain sixteen nonstructural proteins (Nsp1–16). Nsp1 mediates RNA processing and replication and Nsp2 modulates the host cell's survival signaling pathway. Nsp3 separates the translated polyprotein into its distinct proteins. Nsp4 contains transmembrane domain 2 (TM2) and modifies ER membranes. Nsp5 participates in the polyprotein processing during replication. Nsp6 is a putative transmembrane domain. A heterodimer of Nsp7 and Nsp8 significantly increases nsp12 and template-primary RNA combination. Nsp9 participates in viral replication by acting as an ssRNA-binding protein. Nsp10 is crucial for cap methylation of viral mRNAs. Nsp11 is identical to the first segment of Nsp12 and its function is unknown. Nsp12 contains RNA-dependent RNA polymerase (RdRp), a critical component of coronavirus replication/transcription. Nsp13 binds to ATP and the zinc-binding domain of Nsp13 is involved in replication and transcription. Nsp14 is an exoribonuclease domain. Nsp15 has Mn (2+)-dependent endoribonuclease activity. Nsp16 is a 2'-O-ribose methyltransferase [24]. Entry of coronaviruses into host cells is mediated by an increase in glycoprotein (S protein) [16, 25, 26]. Transmembrane spike glycoproteins form homotrimers that protrude from the viral surface. The spike glycoprotein is critical for the entry of coronaviruses, thus making it an attractive antiviral target. A six-helical bundle (6-HB) is formed by HR1 and HR2 which are vital for spike protein-dominated membrane fusion of SARS-CoV or SARS-CoV-2, making HR1 and HR2 a promising drug target [27, 28]. The spike protein of SARS-CoV-2 contains a receptor binding domain that specifically recognizes the ACE2 receptor. The receptor-binding domain is a critical target for antiviral compounds and antibodies [29].

Most patients with COVID-19 develop symptoms such as dyspnea, fever, dry cough, muscle pain, fatigue and diarrhea. However, the rate of complications such as sepsis, septic shock and multiple organ dysfunction syndrome (MODS) has been found to range between 2 and 20% in line with the data collected to date [30–32]. Pathophysiological findings in the lungs, which are the entry route of the virus, show embolisms caused by thrombus formation at the micro and macro level associated with extensive endothelial involvement, as well as intra-alveolar hyaline membranes and alveolar edema [33]. Widespread pulmonary damage is attributed to a cytokine storm that shows local and then systemic effects, together with the damage that starts directly with the virus-ACE2 receptor relationship [34].

3. ACE2

ACE2 cleaves Ang II to angiotensin [1–7], which produces vasodilating, anti-inflammatory and anti-fibrotic effects via binding to the Mas receptor [35–37]. Tissue-bound or membrane-bound ACE2 is a type of transmembrane protein with a single metalloprotease active site and a transmembrane domain [38, 39]. ACE2 is expressed in virtually all human organs in varying degrees. ACE2 expression is present in type II alveolar cells (AT2), respiratory epithelial cells, bronchial transient epithelial secretory cells, myocardial cells, endothelial cells and artery smooth muscle cells, esophagus epithelial cells, tongue epithelial cells, neurons and glia, stomach, cholangiocytes, adipose tissue, pancreatic exocrine glands and islets, bladder urothelial cells, renal proximal tubule cells, podocytes, testis (Leydig and Sertoli cells and spermatogonia), uterus epithelial cells, ovary and breast, maternal–fetal interface, enterocytes from ileum and colon and rectum cells [40, 41]. In the lung, ACE2 is abundantly expressed by Clara cells, type I and II alveolar epithelial cells, macrophages, bronchial epithelium, endothelium, and vascular smooth muscle cells [42].

ACE2 is encoded on chromosome Xp22 and spans 39.98 kb genomic DNA. This gene generates two transcripts originating from the same 805 amino acid residue protein: one transcript consisting of 18 exons and 17 introns (transcript length: 3339 bps), and the other consisting of 19 exons and 18 introns (transcript length: 3507 bps). The ACE2 gene displays high levels of polymorphism; in fact, some single nucleotide polymorphisms (SNPs) of this gene have been reported to be associated with susceptibility to diseases such as hypertension and type 2 diabetes [43, 44].

Single-cell RNA sequencing analysis has shown that ACE2 mRNA is expressed at a higher level in the Asian population than in the Caucasian and African-American populations, and also Asian men have a higher ACE2 mRNA expression compared to Asian women [45, 46].

There is a negative correlation between ACE2 expression and COVID-19 severity. ACE2 is secreted from membranes at different levels. Two cell membrane proteases are important for this secretion: transmembrane protease serine 2 (TMPRSS2) and protein 17 (ADAM17) containing disintegrin and metalloproteinase domain [47].

More specifically, ADAM17 acts directly on ACE2 and leads to the shedding of ACE2 into the extracellular cellular space, whereas TMPRSS2 affects not only ACE2, but also the S protein of SARS-CoV-2, resulting in membrane fusion and cellular uptake of the virus. As a result of an extensive database analysis, Cao et al. identified 1700 variants in the ACE2 gene region on the X chromosome. They identified 15 (14 SNPs and 1 insertion/deletion (INDEL)) uniquely expressed variants with higher minor allele frequencies (MAF) in the Asian population than in the European population [48].

It is still debated whether these differences should be taken into account in epidemiological studies on COVID-19, which includes ethnic associations with disease development [49]. Importantly, diseases correlated with high levels of SARS-CoV-2 infection, such as hypertension and diabetes, have been found to have a lower expression of ACE2 in relation to the SNPs in the ACE2 genes.

Individuals with rs383510/T and rs2070788/G genotypes of TMPRSS2 located on chromosome 21q22.3 were found to be more prone to develop a severe form of influenza A (H1N1) and acute respiratory distress syndrome (ARDS) [50]. Remarkably, males have been shown to be more likely to develop severe H1N1 influenza [51].

The ADAM17 gene region on chromosome 2p25.1 has been determined to differ in allele profiles between Asian and European populations and these SNPs are associated with hypertension [52] and/or sepsis [53].

When the S1 protein, located at the spikes of SARS-CoV and SARS-CoV2, attaches to the enzymatic domain of ACE2 on the cell membrane, both the virus and the enzyme are taken up into the host cell by endocytosis [54, 55]. This led to the idea that lowering the amount of ACE2 in cells could help fight against coronavirus infection. As an antithesis to this, ACE2 has also been shown to have a protective effect against viral lung injury by increasing the production of the vasodilator angiotensin 1–7. Also, some studies in mice have demonstrated that the interaction of the coronavirus terminal protein with ACE2 causes a reduction in ACE2 levels in the cell membrane, with the protein being pulled into and degraded, and therefore may increase lung damage [56].

Studies in rodents have shown that both ACE inhibitors and angiotensin receptor blockers (ARBs) used to treat high blood pressure increase the amount of ACE2 and therefore may increase the severity of coronavirus infections [57]. However, scientific societies have recommended continuing standard ACE inhibitor and ARB treatment [58]. A systematic review and meta-analysis published on July 11, 2012

found that the use of ACE inhibitors resulted in a 34% reduction in pneumonia risk compared to controls. Besides, it was observed that the risk of pneumonia is reduced by treatment with ACE inhibitors in patients with a high risk of pneumonia, especially those with stroke and heart failure [59].

ACE2 limits the adverse vasoconstrictor and profibrotic effects of AngII. Hydrolysis of AngII to Ang (1e7) reduces the oxidative stress of AngII on endothelial cerebral arteries. Disruption of ACE2 results in increased AngII levels and impaired cardiac function. Decreased cardiac ACE2 levels have been reported in hypertension (HT) and diabetic heart disease, and low ACE2 mRNA expression has been associated with HT, dyslipidemia, and/or heart failure [60, 61].

It was reported that ACE2 gene polymorphisms can influence both susceptibility to SARS-CoV-2 and the prognosis of COVID-19 disease. The S1 domain of the SARS-CoV2 spike protein mediates its binding to the ACE2 receptor site, while the S2 domain mediates membrane fusion at the membrane-associated portion undergoing postbinding transconformational modifications. In a study conducted by Li et al. in rats, they produced a conformational change in the ACE2 α -helix 1 structure by changing the His353 amino acid of the ACE2 receptor and modifying a glycosylation site (Asp 90), and as a result, they determined that this receptor became more suitable for the binding of SARS-CoV [62]. They also found that Leu584Ala, a point mutation in ACE2, significantly increased the binding of the enzyme, thus facilitating the entry of SARS-CoV into target cells [63]. In some studies, ACE2 expression was found to be low in cells infected with SARS-CoV, and recombinant SARS-CoV spike protein decreased ACE2 expression and thus increased lung damage [64, 65]. In a study by Cao et al. in different populations, seven of the 32 ACE2 variants (Lys26Arg, Ile486Val, Ala627Val, Asn638Ser, Ser692Pro, Asn720Asp and Leu731Ile/Phe) were found to be effective for SARS-CoV2 [48].

In one study, Stawiski et al. reported that while human ACE2 variants K26R, T27A, N64K, S19P, I21V, E23K, T92I, Q102P and H378R are predicted to increase host susceptibility, other ACE2 variants K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L and D509Y are putative protective variants predicted to show decreased binding to SARS-CoV-2 S-protein. Among these, T92I variant, part of a consensus NxS/T N-glycosylation motif, exhibited increased affinity for S-protein [66].

4. Transmembrane serine protease

Transmembrane protease serine type 2 (TMPRSS2) belongs to the type II transmembrane serine protease family. It facilitates the entry and activation of the virus by making proteolytic cleavage in the spike protein. After SARS-CoV binds to ACE2, proteolytic cleavage of the S protein via the cysteine protease cathepsin B/L or TMPRSS2 is required for the virus to enter the cell. Although both activate the SARS CoV Spike protein, TMPRSS2 activity has been shown to be required for the spread of the virus in the host. While rodents given TMPRSS2 serine protease inhibitor were protected from SARS-CoV, the same effect was not observed in those given cathepsin B/L cysteine prosthetic inhibitor [67]. The transmembrane serine protease TMPRSS2 is an essential enzyme capable of degrading the hemagglutinin of many influenza virus subtypes and coronavirus S protein [68, 69]. Studies have shown that mice with TMPRSS2 deficiency are more resistant to infections with H1N1 and H7N9 influenza A virus [68, 70]. TMPRSS2 has been demonstrated to help SARS-CoV-2 enter host cells by cleaving the S protein [20]. Matsuyama et al. showed that cell lines expressing TMPRSS2 are highly susceptible to MERS-CoV, SARS-CoV and SARS-CoV-2 [71]. The gene encoding TMPRSS2 is polymorphic and

is regarded as a susceptibility gene for H1N1 and H7N9 influenza [50]. TMPRSS2 is expressed in numerous tissues that are targets of COVID-19, such as the lung, heart, kidney, and digestive tract. It is also expressed in microvascular endothelial cells, suggesting that it may play a role in endothelial dysfunction, thrombosis and related complications. TMPRSS2 variants are also thought to contribute to the clinical diversity of COVID-19. In the study of Asselta et al., it was reported that TMPRSS2 exonic variant p.Val160Met and two haplotypes were detected more frequently in the Italian population than in East Asians [72]. Besides, in another study, the presence of TMPRSS2-ERG fusion in prostate cancer and the strong regulation of TMPRSS2 by androgens led to the hypothesis that TMPRSS2 could partly explain the greater involvement of males in the COVID-19 pandemic [73].

5. Elastase

SARS-Cov-2 enters the cell by binding its S protein with cellular receptors [20]. Some proteases, such as TMPRSS2, cathepsin L, neutrophil elastase, and probably TMPRSS11A are involved in this process. As a matter of fact, polymorphisms in their encoding genes could not only have an impact in the expression and/or structure of these proteases but also be associated with susceptibility to SARS-CoV-2 infection. Elastase is secreted by neutrophils as part of an inflammatory response to a viral infection and is also produced by opportunistic bacteria that can colonize virally infected respiratory tissue [74]. Increased elastase activity as a result of the aberrant inflammatory process produces considerable pulmonary damage that contributes significantly to the pathogenesis of chronic obstructive pulmonary disease, cystic fibrosis, ARDS and pulmonary fibrosis [75, 76]. Moreover, the dramatic increase in neutrophil elastase (NE) in severe COVID-19 may be related to neutrophil activation by the IL-8/CXCR2 pathways [77]. The ELANE gene encoding neutrophil elastase is located on chromosome 19p13.3. Two transcripts have been reported for this gene, which produce consensus coding sequence. The first transcript contains 5 exons and 4 introns and 5 exons encode this 267 amino acid protein (transcript length, 909 bps). The second transcript consists of 6 exons and 5 introns, and 5 exons encode this 267 amino acid protein (transcript length, 1028) [78]. In the ELANE gene, 12 polymorphisms with potential functional effects were identified: ten in the promoter region, two in the 5' region near the gene and two in the 3' region near the gene. These 12 polymorphisms produce binding sites for various transcription factors and microRNAs [78].

The levels of NE expression are known to be affected by the polymorphisms in the promoter region of the neutrophil elastase (ELANE) gene. Several polymorphisms were identified to date in the six repetitive tandem motifs of the ELANE gene promoter region: -903 T/G, -741G/A, -832G/T, -789C/T, and extra 52 bp between the fourth and fifth repeats. Polymorphisms -903 T/G and -741G/A have been associated with risk of lung cancer [79]. Luciferase activity assays have shown higher activity for ELANE gene promoter constructs carrying -903 T/-741G compared to the constructs carrying -903G/-741A. Based on these findings, predicted activity of ELANE genotypes was classified as low (-903TG), intermediate (-903TT/-741AG and -903TT/-741AA), or high (-903TT/-741GG) [80].

6. Cathepsin L

Cathepsin L is a peptidase that cleaves peptide bonds, preferably with aromatic residues at the P2 position and hydrophobic residues at the P3 position [81]. It was

reported previously that cathepsin L participates in the viral glycoprotein processing of Ebola virus and SARS-CoV, and this viral process has been found to be critical for cell membrane fusion and host cell entry [82]. Using cathepsin B and L inhibitors in HEK 293/hACE2 cells, Ou et al. showed that treatment with cathepsin L inhibitor reduced the entry of SARS-CoV-2 into cells [21]. This finding suggests that cathepsin L may be crucial for S protein priming in the lysosome for viral entry.

Six polymorphisms with possible functional implications were identified in the cathepsin L gene. These polymorphisms have been found in various regions of the gene and form binding sites for transcription factors [78]. Among these polymorphisms, rs41307457 has a high frequency only in the African population and rs41312184 is present with a high frequency especially in the European population. The authors suggested that the relationship of these polymorphisms with SARS-CoV-2 infection should be analyzed in these populations [78].

7. Human alpha-1 antitrypsin (A1AT)

Human alpha-1 antitrypsin (A1AT) is a 52 kDa glycoprotein synthesized in the liver and circulates in the blood, and is a natural inhibitor of several proteases. Adequate A1AT activity is crucial for the prevention of proteolytic tissue damage [83]. In people with one of many inherited mutations in A1AT, low circulating A1AT levels increase the risk of devastating diseases, particularly emphysema [84]. Infusion of plasma-purified A1AT protein has proven therapeutic benefits in patients with A1AT deficiency [85]. The pharmacokinetics and safety of A1AT have been well studied. It was accepted as safe with its rare and generally well tolerated side effects [86]. Studies have shown that human A1AT has both anti-inflammatory and anti-SARS-CoV-2 viral effects [87]. This dual role makes it a unique and excellent candidate for the treatment of COVID-19. Alpha-1-antitrypsin (AAT) is a serine protease inhibitor (SERPIN) and the third most abundant circulating protein. AAT plasma level may increase 3 to 5-fold in states of systemic inflammation and/or infection, perhaps an indication of the homeostatic role of AAT, but has been found to be insufficient in severe cases of COVID-19 [88, 89]. Alpha-1-antitrypsin (AAT) has been shown to antagonize various pathophysiological mechanisms induced by SARS-CoV-2. It has been demonstrated that these pathophysiological mechanisms inhibit TMPRSS-2, the host serine protease that degrades the spike protein of SARS-CoV-2, SARS-CoV-2 [20]. AAT also has antiviral activity against other RNA viruses, influenza and HIV. It also induces autophagy, a known host effector mechanism against MERS-CoV, a related coronavirus that causes Middle East Respiratory Syndrome [90]. Additionally, AAT has potent anti-inflammatory properties, in part by inhibiting both nuclear factor-kappa B (NF κ B) activation and ADAM17 (also known as tumor necrosis factor-alpha converting enzyme) and may therefore reduce the hyperinflammatory response to COVID-19 [91]. Moreover, AAT inhibits neutrophil elastase, a serine protease that helps recruit potentially harmful neutrophils and is implicated in acute lung injury [92]. AAT inhibition of ADAM17 prevents ACE2 from being scavenged, thus preserving ACE2 inhibition of bradykinin and reducing bradykinin's ability to cause capillary leakage in COVID-19 [93]. AAT also inhibits thrombin and venous thromboembolism, and microthrombi and macrothrombi in situ are increasingly recognized to play a role in COVID-19 [94]. Furthermore, AAT inhibition of elastase results in the formation of neutrophil extracellular traps (NETs), a complex extracellular structure composed of neutrophil-derived DNA, histones, and proteases, and involved in the immunothrombosis of COVID-19 can antagonize. In fact, AAT has been shown to alter the shape and adherence of NETs not associated with COVID-19 [95]. AAT inhibition of endothelial cell apoptosis may

also limit endothelial damage associated with severe COVID-19-related acute lung injury, multi-organ dysfunction, and preeclampsia-like syndrome in gravid women [96]. Although it is well known that alpha 1 antitrypsin deficiency is quite common in Europeans, rs17580 is the most common deficiency variant as reported by most of the studies conducted to date [97].

8. HLA

Human leukocyte antigens (HLA) are encoded by major histocompatibility complex (MHC) genes and are highly polymorphic. MHC molecules act as receptors for viral peptides. Studies have shown that polymorphisms in the HLA region are associated with susceptibility to many common infectious diseases [98]. In a study conducted in 28 patients with severe respiratory failure, HLA-DR expression was found to be very low, suggesting that HLA is an important immune regulator in COVID-19 [99]. In addition, several studies have attempted to determine HLA alleles that are associated with increased or reduced susceptibility. HLA genes are important in olfactory perception. Loss of sense of smell differs among individuals who had COVID-19 [100]. The olfactory receptor gene is located at the same locus as the MHC and is co-transmitted [101]. Therefore, variations in HLA genes are known to play a role in differences in immune response against pathogens.

9. Conclusion

Today, many genetic polymorphisms are known to be involved in pathways that play an important role in the attachment of the microbiological agent to the host cell, resulting in variations in the susceptibility to disease and disease severity. Currently, genetic polymorphisms are used in molecular medicine for many purposes. Better understanding of the mechanisms caused by genetic polymorphisms is expected to allow for the development of new treatments and discovery of preventive drugs. The COVID-19 pandemic shows marked geographical differences in its prevalence and mortality. This variability may be due both to the presence of several subtypes of the virus and to genetic differences in human populations. Given this fact and the important roles of ACE2, TMPRSS2, cathepsin L and elastase in the process of virus entry into the host cell, this article aims to suggest possible variants at these loci for genetic association studies in SARS patients. Although there appears to be a multifactorial genetic influence on the risk of SARS-Cov-2 infection and possible disease severity, SNP profiling of the ACE2, ADAM17 and TMPRSS2 genes is recommended to identify potentially vulnerable populations at risk with a relatively simple and easy-to-perform test such as PCR [102] or MASSarray [103]. Thus, a 'multiSNP risk score' applicable to large populations can be determined, and therefore it may be possible to identify subjects carrying a combination of fewer suitable alleles for ACE2, ADAM17 and TMPRSS2. Such an analytical strategy has recently been developed based on patient genetics for immunogenetic profiling designed to individualize immunotherapy [104]. It is known that macrophage activation syndrome (MAS) is an important cause of mortality and morbidity in patients with COVID-19. In a study investigating gene polymorphisms in the pentraxin 3 (PTX3), a molecule that is synthesized by a number of inflammatory cells and considered to be associated with mortality, MAS was found to be less common in COVID-19 patients with the AG genotype (rs1840680 (1449A/G) polymorphism) and PTX3 levels were higher in patients carrying the A allele [103]. In a study on interferon-induced membrane protein-3 (IFITM-3) gene variants,

an established risk factor in severe viral infections, the IFITM3-SNP, rs12252-G allele was found to be significantly associated with hospitalization and mortality in COVID-19 patients and lower IFN γ levels were lower patients with the AG/GG genotype [105]. Homocysteine can be used as a potential biomarker to predict the severity of a number of infections in COVID-19. A study in the Latino population suggested that the MTHFR 677 T allele may contribute to the mortality from COVID-19 [106]. Dipeptidylpeptidase-4 (DPP4) is known to be a key protein for the entry of SARS-CoV-2 into the host cell as well as in obesity and hypertension, which are associated with worse prognosis in COVID-19. In light of these data, a study suggested that the DPP4 rs3788979 polymorphism might be a risk factor for COVID-19 disease [107]. Recently, in a south Asian population, the frequency of Human leukocyte antigen (HLA) variants HLA-B*51 and HLA class II, DRB1*13 was found to be high in patients with fatal COVID-19 [108].

In summary, until now, genetic influences on the interindividual susceptibility of COVID-19 have been largely underestimated; therefore, we hope that this review will fill this gap and pave the way for validation in studies at the experimental and clinical levels. Taken together, these data suggest that several gene variants may have an effect on susceptibility to COVID-19 disease, its prognosis and possibly the efficacy of vaccines. As SARS-CoV-2 continues to threaten global health, it is essential to elucidate the molecular mechanisms involved in this infection to develop specific treatment and prevention strategies.

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