Gene Expression **2023** vol. 22(3) | 222–231
DOI: 10.14218/GE.2023.00026

Review Article

Host Genetics and COVID-19: Genes Underlying the Patterns of Susceptibility and Prognosis

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Received: May 09, 2023 | **Revised:** June 25, 2023 | **Accepted:** August 24, 2023 | **Published online:** September 21, 2023

Abstract

Host-specific genetics, such as epigenetic profiles and genetic variants, can contribute to the pathogenesis of infectious diseases. Strong associations have been previously identified in infections by human immunodeficiency virus (HIV), *Plasmodium falciparum*, norovirus, and influenza A virus. Despite the efforts to characterize the role of host genetics in severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2) infection, this comprehension remains incipient. Coronavirus disease 2019 (COVID-19) can evolve with a wide spectrum of manifestations, ranging from asymptomatic and mild cases to severe forms with acute respiratory distress syndrome, multi-organ complications, and even death. Classic clinical risk factors only partially explain this interindividual variability, suggesting that host genetics may contribute to the heterogeneity of courses. Robust evidence has revealed the multiple associations of genes (*ABO*, *PPP1R15A*, *SLC6A20*, *IFNAR2*, *OAS*, *TYK2*, *CCR2*, *CCR5*, *TLR7*, *ApoE*, *TMPRSS2*, *HLA*, *ACE2*, *etc.*) with the susceptibility and/or severity of SARS-CoV-2 infection. In addition, the genetics behind the established risk factors have been considered: at least four loci associated with COVID-19 severity (*DPP9*, *FOXP4*, *SFTPD* and *MUC5B*) have been previously linked to lung fibrosis, interstitial lung disease, lung carcinomas, and/or decreased lung function. In summary, identifying the host-specific genetic factors may improve our knowledge of risk groups for infection and severe outcomes, as well as the biological mechanisms of therapeutic relevance. Therefore, the present literature review aims to understand the genetics underlying the patterns of susceptibility and prognosis of COVID-19.

Keywords: Epigenetic; Genes; Genetic polymorphism; Genetic susceptibility; SARS-CoV-2.

Abbreviations: ACE, angiotensin-converting enzyme; Ang, Angiotensin; *ApoE*, apolipoprotein E; *CCR2*, C-C chemokine receptor 2; *CCR5*, CC-chemokine receptor 5; COVID-19, coronavirus disease 2019; *CpG*, cytosine-phosphate-guanine; DNAm age, DNA methylation age; *DPP9*, dipeptidyl peptidase 9; EMT, epithelial–mesenchymal transition; *FOXP4*, Forkhead box P4 protein; *FUT2*, fucosyltransferase 2; GWAS, genome-wide association studies; HIV, human im munodeficiency virus; *HLA*, human leukocyte antigen; IFN, interferon; *IFNAR2*, interferon alpha and beta receptor subunit 2; IL, interleukin; *LZTFL1*, Leucine Zipper Transcription Factor Like 1; miRNAs, microRNAs; *MUC5B*, mucin 5B; *OAS*, 2′-5′-oligoadenylate synthetase; SARS-CoV-2, severe acute respiratory syndrome virus coronavirus 2; *SFTPD*, surfactant protein; siRNA, small interfering RNA; SNP, single nucleotide polymorphism; *TLR7*, toll-like receptor 7; *TMPRSS2*, transmembrane protease serine 2; *TYK2*, tyrosine kinase 2.

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How to cite this article: Khouri BF, de Souza Candido IP, Poli-Frederico RC, Bignardi PR. Host Genetics and COVID-19: Genes Underlying the Patterns of Susceptibility and Prognosis. *Gene Expr* 2023;22(3):222–231. doi: 10.14218/GE.2023.00026.

Introduction

In December 2019, health facilities in Wuhan, Hubei Province, China reported an outbreak of unusual viral pneumonia, in which the cause was unknown.[1] Human airway epithelial cells in samples obtained from patients with the condition were used to isolate the new coronavirus: severe acute respiratory syndrome virus coronavirus 2 (SARS-CoV-2).[1] Highly transmissible, the coronavirus disease 2019 (COVID-19) spread quickly worldwide, and on 11 March 2020, the World Health Organization announced a global pandemic.[1,2]

Some individuals who come into contact with the pathogen become infected, while others do not (susceptibility phenotype).[3] Among the infected individuals, the disease developed with varying degrees of severity (severity phenotype): COVID-19 can evolve with various types of manifestations, ranging from asymptomatic and mild forms, to severe disease with respiratory failure, multi-organ complications, and even death.[3–5] This interindividual variability was only partially explained through classic clinical risk factors, and in certain cases, the courses of the disease were more severe or milder than the acquired risk factors would expect. Based on this, it was assumed that the contribution of host genetics, as a component of its multifactorial etiology, plays an essential

role in its heterogeneity of courses.[3]

A study conducted in 1988 on a Danish population followed 960 families, which had children who were adopted before turning seven years old. The relative risk of dying of the adopted child due to certain causes was assessed in the context that one of the biological or adoptive parents would die due to the same cause before the age of 50. Adopted children have a 5.81-fold risk of dying due to infection when the biological father dies due to an infectious disease (the relative risk is greater than that associated with heart, cerebrovascular and oncological diseases for the biological father). The risk would not be significant when the adoptive parent dies from an infection. These findings highlight the probable heritability of the predisposition to infectious diseases.[6,7]

Indeed, several examples of important genetic relationships associated with the susceptibility and evolution of infectious diseases have been studied, and repeatedly validated in the literature, similar to the case of infection by human immunodeficiency virus (HIV), *Plasmodium falciparum*, and norovirus.[6,8–12]

In the case of HIV infection, the presence of an altered CC-chemokine receptor 5 (CCR5) co-receptor, that is, the CCR5 Δ 32 mutation, hindered the entry of viral T cells, leading to the slower progression to acquired immunodeficiency syndrome.[6,8] For infections by *Plasmodium falciparum*, the protective effect of the sickle allele of the hemoglobin-β gene in heterozygous individuals has been well-described.[6,9,10] The fucosyltransferase 2 (FUT2) genotype has also been shown to have a protective effect on the susceptibility to norovirus infections. The cells that line the human gastrointestinal tract have surface blood group antigens (ABO system). Since the FUT2 mutant produces intestinal lining cells that do not present these antigens, individuals with this phenotype are non-secretors, generating protection against the infection by norovirus strain GII.[4,6,11,12]

The importance of identifying host-specific genetic factors remains undeniable, because this can elucidate the causal relationships between risk factors, and delineate the biological mechanisms of therapeutic relevance. However, for the genetic basis involved in COVID-19, much remains unknown, and various gaps in already acquired knowledge require further studies to better understand these. Therefore, the present narrative review aims to understand the genetics underlying the patterns of susceptibility and prognosis of COVID-19.

Genetic variants associated with COVID-19

Since 2020, genome-wide association studies (GWAS) on COVID-19 have provided the conditions to partially elucidate the role of host genetics behind the SARS-CoV-2 infection.[13,14] It is known that GWAS have limitations, such as the sample size, and the fact that these may present with an exaggerated representation of cases with unfavorable outcomes, given that, in most cases, these were selected in medical clinics and hospitals (individuals have enough clinical manifestations to seek medical care), among other confounding factors. However, these GWAS have identified several reproducible associations, serving as a basis for further projects, including cohort and case-control studies performed for different populations from multiple countries.[15]

The GWAS and meta-analysis published in May 2023 analyzed 24,202 cases of critical COVID-19, which comprised a combination of microarray genotypes, whole genome sequencing data from the GenOMICC study (n = 11,440), and data obtained from the ISARIC4C (n = 676 cases) and SCOURGE (n = 5,934 cases) studies. This study identified 49 genetic associations with critical COVID-19, including the following nearest genes: *SLC2A5*, *JAK1*, *AK5*, *EFNA4*, *TRIM46*, *THBS3*, *HCN3*, *BCL11A*, *SLC6A20*, *LZTFL1*, *NXPE3*, *PLSCR1*, *ANAPC4*, *ARHGEF38*, *IRF1-AS1*, *CCHCR1*, *LTA*, *HLA-DQA1*, *FOXP4*, *HIP1*, *ZKSCAN1*, *RAB2A*, *IFNA10*, *AQP3*, *ABO*, *SFTPD*, *MUC5B*, *ELF5*, *OAS1*, *FBRSL1*, *ATP11A*, *SLC22A31*, *PSMD3*, *KANSL1*, *TAC4*, *DPP9, TYK2*, *PDE4A*, *FUT2*, *NR1H2*, *CASC20*, *IFNAR2*, *IL10RB*, *ATP5PO*, *TMPRSS2*, and *ACE2*. Among these genes, 16 genes were not previously reported.[16]

A meta-analysis organized by the COVID-19 Host Genetic Initiative combined the genetic data obtained from 46 studies (with a total of >2 million people).[17] The results of that study provided evidence for 13 independent significant genome-wide loci associated with COVID-19, which included both susceptibility and severity.[17] The COVID-19 Host Genetic Initiative discoveries support that the *ABO* loci (in the 9q34.2 region) and *PPP1R15A* (in the 19q13.33 region), in addition to *SLC6A20* (in the 3p21.31 region), can indeed affect the susceptibility to infection.[17] Apparently, the strongest signal associated with susceptibility was the *ABO* gene (rs912805253).[18,19]

In the age- and sex-adjusted meta-analysis performed by the Severe COVID-19 GWAS group, an increased risk was identified in individuals with blood group A, when compared to the other blood groups (odds ratio = 1.45, 95% CI = 1.20–1.75), and a protective effect was identified in individuals with blood group O, when compared to the other blood groups (odds ratio = 0.65; 95% CI = 0.53–0.79).[17] Corroborating these findings, another meta-analysis, which included 23,285 COVID-19 cases and 590,593 controls, concluded that individuals with blood group A are more susceptible to SARS-CoV-2 infection, and that individuals with blood group O are less susceptible to COVID-19.[20]

In line with this, a study conducted on 265 patients infected with SARS-CoV-2 in China revealed that the proportion of blood group A patients with COVID-19 was higher than that in healthy controls (p = 0.017). In turn, the proportion of blood group O infected patients was significantly lower, when compared to healthy controls (p < 0.01).[21] The pathophysiological mechanism involved in this association remains unknown, but studies have suggested that the protective effect against SARS-CoV-2 infection is exerted by anti-A IgG antibodies.[18] The association of the *ABO* variant with higher levels of CD209 protein, which interacts with the COVID-19 protein spike, was also described.[18]

At least two mechanisms correlate to severe disease in COVID-19: innate antiviral defenses (interferon alpha and beta receptor subunit 2 [*IFNAR2*] and *OAS* [2′-5′-oligoadenylate synthetase] genes) and host-induced inflammatory lung injury (dipeptidyl peptidase 9 [*DPP9*], tyrosine kinase 2 [*TYK2*], and C-C chemokine receptor 2 [*CCR2*]).[22] For the variant that encodes *DPP9* on chromosome 19p13.3, it is important to emphasize that variants in this locus are associated with idiopathic pulmonary fibrosis.[22] In turn, *CCR2* promotes the chemotaxis of monocytes and macrophages toward the sites of inflammation.[22]

The increase in expression of interferon receptor subunit IFNAR2 was associated with lower odds of developing severe forms of COVID-19, which was explained by the beneficial role of type I interferon.[22,23] Exome sequencing has identified hemizygous mutations in the toll-like receptor 7 (TLR7) gene on the X chromosome (a single gene condition that reduces the effect or production of type I interferon) as the cause for extremely severe disease in two pairs of siblings: these siblings required ventilatory support for an average duration of 10 days, and stayed in the intensive care unit for an average duration of 13 days; one of the siblings died.[24]

Based on this, it was suggested that the administration of synthetically produced type I interferon can be used to reduce the likelihood of severe disease, since this has been used for treating iso-

lated cases of individuals with defects in its production.[3] An article published in 2021 reported the administration of a single dose of subcutaneous injection of Peg-IFN-α2a (Pegasys, at a dose of 1.5 μg/kg) in two subjects with COVID-19, who had inborn errors that affected the production of type I interferons (IFNs): both subjects presented with a rapid resolution of manifestations on admission after the administration of Peg-IFN-α2a.[25]

In the 3p21.31 region, a single nucleotide polymorphism (SNP, rs17713054G>A) was identified, which interacted with the promoter of the Leucine Zipper Transcription Factor Like 1 (*LZTFL1*) gene, conferring a gain-of-function. The same study, which conducted a transcriptomic analysis of 46 areas of postmortem lung biopsies obtained from three subjects with critical COVID-19, reported the widespread epithelial dysfunction and alveolar damage with reorganization, suggestive of the infection response pathway regulated by *LZTFL1*, the epithelial-mesenchymal transition (EMT). In the context of an acute viral infection, EMT leads to the reduction of ACE2 and TMPRSS2, which are both cell receptors of SARS-CoV-2. These decrease the infection efficiency and allow epithelial cells to proliferate and repair damaged tissues. *LZTFL1* is a known EMT inhibitor, and the increased risk of respiratory failure in patients with SARS-CoV-2 infection associated with the 3p21.31 locus has been justified. Due to this, *LZTFL1* may be considered as a therapeutic target.[26]

A study that was carried out in Italy evaluated a sample recruited in 2021, which comprised 381 COVID-19 patients with varying degrees of severity (207 patients with moderate or severe disease, and 174 patients with asymptomatic or paucisymptomatic infection) and 420 healthy controls. In this population, it was found that a variant of the *LZTFL1* gene (rs35044562A>G) was associated with the unfavorable disease course ($p = 0.001$).[27]

The data on the polymorphisms of eight genes were analyzed for risk of COVID-19 infection and severity: *HLA*, *ABO*, angiotensin-converting enzyme 1 (*ACE1*), angiotensin-converting enzyme 2 (*ACE2*), *apolipoprotein E* (*ApoE*), *CCR5*, transmembrane protease serine 2 (*TMPRSS2*), and interferon-induced transmembrane protein 3. The results indicated that variations in the *ApoE*, *ACE*, *TMPRSS2*, *CCR5* and *HLA* genes appeared to be correlated to the susceptibility to and/or severity of COVID-19.[28]

The *ApoE* gene encodes a protein called, apolipoprotein E (ApoE), which plays a crucial role in lipid metabolism and transport. There are three common variants for the *ApoE* gene: ε2, ε3 and ε4. Each variant differs in a few key amino acids, which may affect the protein's function.[29] Studies have suggested that the ε4 variant of the *ApoE* gene may be associated with severe COVID-19.[30,31]

Chen *et al*.[31] suggested that the ε4 allele of the *ApoE* gene is associated with the susceptibility and severity of COVID-19. They investigated two possible molecular links: between ApoE and the spike protein, and between ApoE and the SARS-CoV-2 primary receptor ACE2. The findings suggested that ApoE interacts with the spike protein and ACE2, but no isoform-dependent binding effects were identified.[31,32] Importantly, further studies have revealed that ApoE4 downregulates the ACE2 protein expression, decreasing the conversion of Ang II to Ang 1–7. These findings may provide the potential mechanism that associates ApoE4 with the increased severity of COVID-19.[33,34]

It is noteworthy that much remains to be clarified on its association with the *ApoE* gene. Thus, more research is needed.[35,36] However, these initial findings suggest that there may be a genetic component for COVID-19 severity, and that certain individuals may be more vulnerable to the virus based on their genetic background.

In addition, it is noteworthy that the *ApoE* gene is highly polymorphic. This means that there are a number of gene variations across different populations. This adds another layer of complexity to the relationship between the *ApoE* gene and COVID-19, since different populations may have different genetic risk factors for the virus.

The *TMPRSS2* gene is located on chromosome 21 (21q22.3), and this encodes a protein called, transmembrane protease serine 2, which plays a role in the entry of the SARS-CoV-2 virus into host cells.[37,38] Polymorphisms in the *TMPRSS2* gene, such as rs12329760, have been suggested to play a role in COVID-19 susceptibility and severity.[39] The rs12329760 has been suggested as one of the candidate polymorphisms to justify the high incidence and SARS-CoV-2 infection-related mortality rate in Italians, when compared to other European populations.[40] Yaghoobi *et al*.[41] reported that in Iranian patients, the T allele of rs12329760 can be considered a risk allele for severe COVID-19. In contrast, previous studies on this variant in European populations have suggested that the T allele has a protective effect.[42]

A prospective observational cohort study published in 2023 evaluated 129 Egyptian individuals, which included 58 severe COVID-19 patients, 51 non-severe COVID-19 patients, and 20 healthy controls. The genotypes and allele frequencies were determined for three SNPs: ACE-1 (rs4343), TMPRSS2 (rs12329760), and ACE-2 (rs908004). In comparing the distribution between severe and non-severe COVID-19 patients, the ACE-2 rs908004 G/G genotype was significantly more prevalent in severe patients ($n = 21$), when compared to non-severe patients ($n = 7$), while for the G/T genotype, this was significantly more prevalent in non-severe patients ($p < 0.05$). For the allele distribution, the mutant allele of the ACE-1 rs4343 SNP and wild allele of the ACE-2 rs908004 SNP were more predominant in severe patients, when compared to non-severe patients ($p = 0.005$ and $p = 0.006$, respectively). However, no significant association between the TMPRSS2 rs12329760 genotypes or alleles was identified.[43]

A case-control study that was also published in 2023 evaluated the genotypic distributions of TMPRSS2 polymorphisms in 147 patients with SARS-CoV-2 infection and 33 healthy controls. The expression for rs2070788GA, rs7364083GA and rs9974589AC was significantly higher in the positive group for COVID-19, when compared to the control group ($p = 0.001$; 0.036 and 0.024, respectively).[44]

Human leukocyte antigen (HLA) genetic variants have also been described to affect the prognosis of patients in different viruses, including COVID-19.[45] The HLA system is a remarkably polymorphic region. In addition, viral genetic studies have revealed that mutations in the spike protein of SARS-CoV-2 affect the affinity with HLA molecules.[46] Dieter *et al*.[28] associated the *HLA-B*38* and *HLA-C*6* alleles with severe COVID-19. Similarly, *HLA-A*11* and *HLA-C*4* were associated with forms of severe COVID-19.[47] Figure 1 presents the genes associated with COVID-19 susceptibility and prognosis.

Epigenetic mechanisms and SARS-CoV-2 infection

Notably, in addition to host-derived genetic mechanisms, epigenetic mechanisms have been shown to have an antiviral effect during host infection,[48] such as microRNAs (miRNAs).[49] Host miRNAs may have a role in preventing viral infections by blocking the target pathways necessary for virus penetration into the cell, or viral replication.

miRNAs are noncoding small molecules capable of regulating gene expression, blocking the translation, or mRNA degradation.[50] Due to the function of miRNAs, the study of intracellular pathways impacted by these has been considered to unravel the pathophysi-

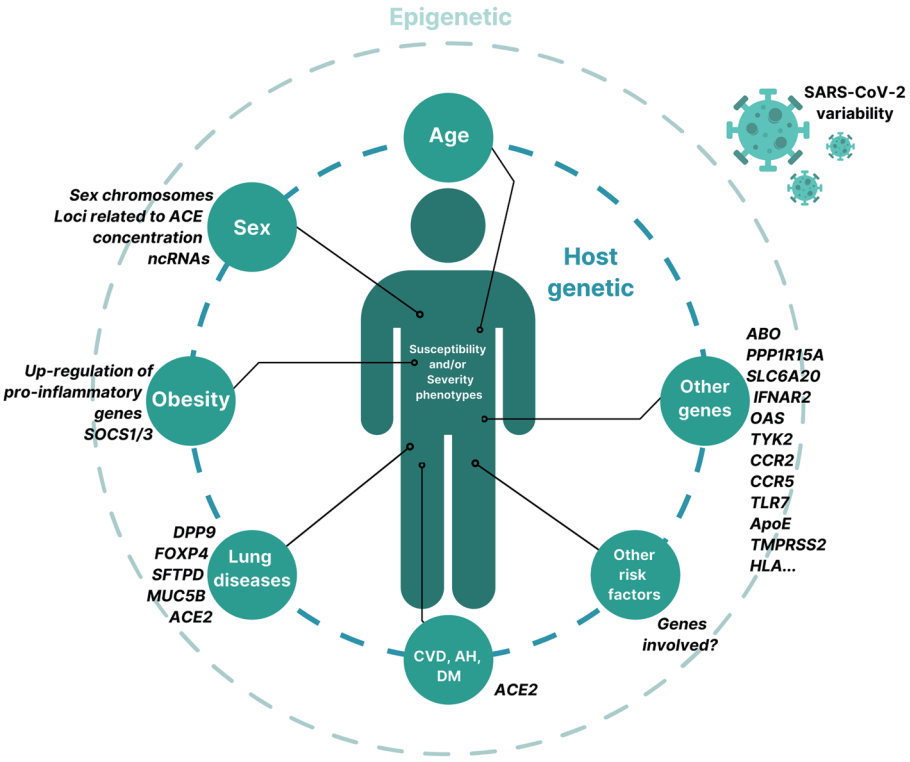

Fig. 1. Risk factors and genes associated with the susceptibility and severity of COVID-19. *ACE2*, angiotensin-converting enzyme 2; AH, arterial hypertension; *ApoE*, apolipoprotein E; *CCR*, CC-chemokine receptor; COVID-19, coronavirus disease 2019; CVD, cardiovascular disease; DM, diabetes mellitus; *DPP9*, dipeptidyl peptidase 9; *FOXP4*, Forkhead box P4 protein; *MUC5B,* mucin 5B; *HLA*, human leukocyte antigen; *IFNAR2*, interferon alpha and beta receptor subunit 2; *OAS*, 2′-5′-oligoadenylate synthetase; SARS-CoV-2, severe acute respiratory syndrome virus coronavirus 2; *SFTPD*, surfactant protein; *TMPRSS2*, transmembrane protease serine 2; *TLR7*, toll-like receptor 7; *TYK2*, tyrosine kinase 2.

ological mechanisms of diseases.[51–54] miRNAs may be the key to understanding viral pathogenesis through the interaction with viral RNA. In the case of SARS-CoV-2 infection, studies have suggested that miRNAs may control SARS-CoV-2 infections through some possible mechanisms. The regulation of the mRNA expression of ACE2 and TMPRSS2, the binding to silence or degrade viral genetic material, and the regulation of anti-inflammatory cytokine genes by suppressing the cytokine storm were suggested by a study.[55] In addition, some epigenetic studies have described some miRNAs involved in the deactivation of ACE2 or TMPRSS2: miR-200b-3p, miR-200c-3p, let-7c-5p, miR-98-5p, let-7 f-5p, miR-4500, and miR-27b.[56,57] Figure 2 presents the mechanisms through which some miRNAs may regulate severe COVID-19.

Considering that miRNA plays a crucial role in the pathogenesis of viruses, it is plausible to assume that COVID-19 can decrease host immune-related circulating miRNAs, and thereby dysregulate immune response.[58] A study reported that circulating miRNAs can inhibit the S protein expression and SARS-CoV-2 replication.[59] In addition, important bioinformatics-based studies have analyzed the role of miRNAs in SARS-CoV-2 infection, and as a potential anti-viral treatment.[60–62] For instance, miR-20a has been described to play a regulatory role in the inflammatory process. A reduction in miR-20a levels in COVID-19 patients was reported by a study, suggesting that these levels can be a potential biomarker of disease severity.[63]

DNA methylation is another epigenetic mechanism that may underlie the complex multifactorial aspect of the host response to SARS-CoV-2 infection.[49] DNA methylation is the covalent binding of a methyl group to the 5′-carbon of cytosine in cytosine-phosphate-guanine (CpG) dinucleotide sequence, which can be regulated by environmental factors, such as diet and microbiome, and this is associated with gene transcriptional repression.[64]

A previous study revealed the inverse relationship between DNA methylation and gene activity in the inflammatory process.[65] Furthermore, a COVID-19 study that involved biological samples from 473 subjects with COVID-19 revealed CD8+ T lymphocytes with various hypermethylated sites, which may be correlated to the inactivation of FCGR3A phagocytosis-related genes, impairing the adequate combat against the virus in patients with severe COVID-19.[66]

DNA methylation can also be modulated by the infection itself.[63] A previous study associated infections during pregnancy with a higher risk of disorders in an offspring's neurodevelopment.[67] Another previous study described the association between changes in DNA methylation and neurodevelopmental disorders.[68] This led a group of researchers from Australia and Brazil to assess the impact of SARS-CoV-2 infection during pregnancy on the neurodevelopment of children born during the COVID-19 pandemic.[69] The preliminary findings from that study revealed that the offspring of mothers exposed to SARS-CoV-2 had a differentially altered methylation of genes in regions correlated to neurodevelopment.[70]

The genetics behind the established risk factors for COVID-19

Epigenetic age impacts

Chronological age is considered one of the most significant risk factors for SARS-CoV-2 infection and severe COVID-19. The fac-

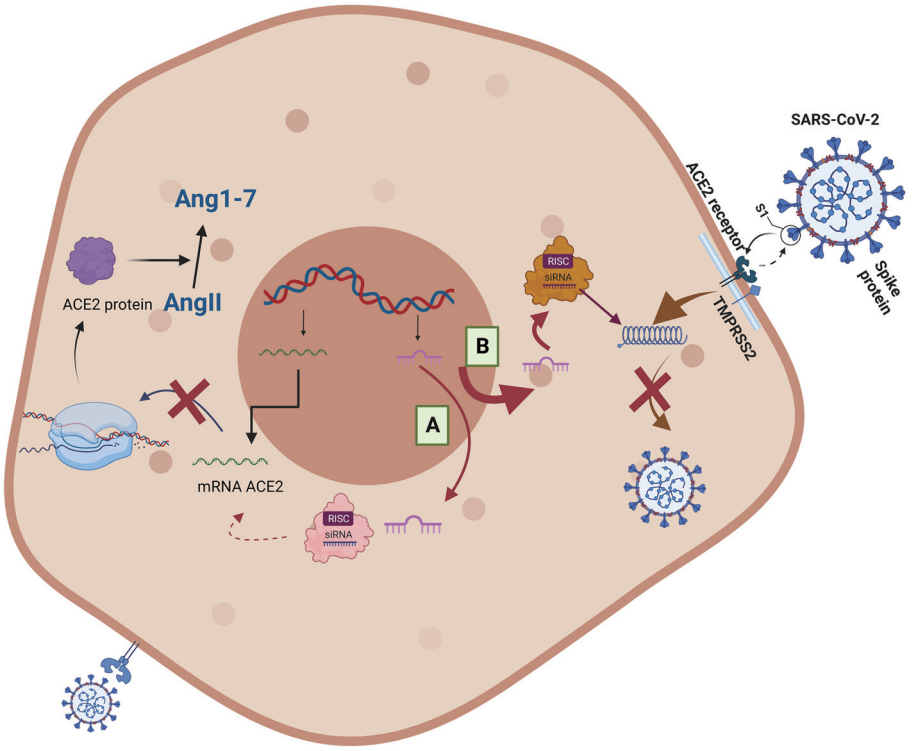

Fig. 2. Mechanisms through which microRNAs (miRNAs) may regulate SARS-CoV-2 infectivity. (a) Destabilization and degradation of mRNA host ACE2 or TMPRSS2, and non-expression; (b) Potential regulatory mechanisms, including the destabilization of viral genomic RNA. Created using Biorender.com. ACE2, angiotensin-converting enzyme 2; Ang, Angiotensin; RISC, RNA-induced silencing complex; SARS-CoV-2, severe acute respiratory syndrome virus coronavirus 2; siRNA, small interfering RNA; TMPRSS2, transmembrane protease serine 2.

tors that justify this relationship include the presence of multimorbidity, frailty, ACE2 alterations, and immunosenescence.[71] Despite these, it was suggested that all these conditions have a common causal factor: the lifetime accumulation of epigenetic changes.[72]

These epigenetic alterations, which manifest as DNA methylation modifications, may be caused by the redistribution of chromatin factors, such as nuclear proteins sirtuin 1/6/7, histone deacetylase 1, and poly [ADP-ribose] polymerase 1, away from regular loci to sites of double-stranded DNA break repair, and subsequently back again, erasing the cellular identity.[72]

Extensive evidence has indicated that age-related changes to the host's epigenome compromise of immune cell function and composition, and negatively impact viral defenses.[72,73] These variations are mostly clearly delineated in the hematopoietic stem cell compartment (the adaptive immune system), while some changes can be observed in the innate compartment.[73] In addition, epigenetic changes impact the methylation regulation of ACE2 and interferon-related pathways.[71]

A study evaluated the DNA methylation in blood samples obtained from 645 patients (with and without COVID-19). The epigenetic clocks and telomere length determine the epigenetic age of an individual's methylation profile. COVID-19 patients presented with DNA methylation age (DNAm age) acceleration for Hannum, PhenoAge, skin-Horvath and GrimAge clocks, and DNAm-based telomere length attrition acceleration, when compared to healthy individuals (all, $p < 0.0001$).[57]

In summary, epigenetic age may be a better biomarker than chronological age for predicting the susceptibility to COVID-19 infection and severe manifestations. Furthermore, it is vital to consider that COVID-19 infection can accelerate the epigenetic age, and that the long-term impact needs to be studied.

Influences of sex chromosomes

Most of the sex differences in susceptibility to infectious diseases have been considered to be caused by the influence of sex hormones on the immune system.[74] Indeed, globally, the male population is more likely to suffer from chronic diseases (diabetes mellitus, arterial hypertension, and coronary heart disease), and gender differences in risky behavior are significant (such as smoking and abusive consumption of alcoholic beverages).[75]

However, in addition to these known and consolidated factors, the idea that sex chromosomes can influence the susceptibility and severity of infectious diseases is gaining increasing recognition.[74,75] This hypothesis has been studied in other pathologies, such as influenza A and HIV infection, with positive associations.[74,76]

A study that used a murine model of influenza A virus infection and a Y chromosome panel in the C57BL/6J background revealed the genetic variation influences in chromosome Y on disease pathogenesis. Specific Y chromosome variants have been associated with increased susceptibility to influenza A virus infection in males, and increased pathogenic immune responses in the lungs, including the activation of γδ T cells that produce pro-inflammatory cytokines (interleukin 17, IL-17), without affecting the replication of the virus.[74]

Another study that included 3,727 males revealed the accelerated progression to acquired immunodeficiency syndrome, and the related death in European Americans among individuals with hap-

logroup I of the Y chromosome. Although the highly active antiretroviral therapy achieved a longer HIV-1 viral suppression for this group, these individuals were more likely to fail the therapy.[76]

For COVID-19, multiple studies have revealed the increased risk of severe COVID-19 in males, when compared to females, with a pooled relative risk estimate of 1.73 (95% CI = 1.50–2.01).[77] Indeed, SARS-CoV-2 infects cells by binding to cell surface receptors that are widely distributed on respiratory tract cells: ACE2.[78] The *ACE2* gene is located on the X chromosome (location: Xp22.2; nucleotides 15 494 402–15 602 148, GRCh38.hg38 version), suggesting a potential for increased expression in females.[75,79] However, studies have reported that the age-adjusted plasma concentrations of ACE2 are higher in males, when compared to females. This difference was especially notable in pathological conditions, such as diabetes and chronic kidney disease.[75,78]

In order to verify the existence of the sex-specific genotypic effects on plasma ACE2 concentrations, a study evaluated the specific and combined genomic associations of plasma ACE2 in 2,420 men and 1,022 women with heart failure (mean age: 70.9 ± 11.6 years old). The results identified three loci associated with plasma ACE2 concentrations of genomic-wide significance in males, but none were identified in females.[78] Among the three identified loci, one loci was a cis-protein quantitative trait loci on chromosome X, which is near the cognate *ACE2* gene, while two trans-loci were identified on chromosomes 12 and 21, which included genes that encode transcription factors HNF1A and ERG.[78,80] The pooled analysis revealed that there were no additional significant loci throughout the genome.[78]

In addition, another study revealed the effects of the profile of non-coding RNAs in male individuals with COVID-19, highlighting that these may play an essential role in influencing cellular processes, and controlling the regulation of gene expression.[81]

Obesity and pro-inflammatory genes

The cytokine storm is described as a set of manifestations secondary to the excessive production of cytokines by the overactivation of the immune system.[82,83] Clinically, this can evolve with complications that arise from multiple organ failure, coagulopathy, and in more severe cases, death.[83,84]

In COVID-19, the cytokine storm is considered as a key pathogenetic factor correlated to disease severity.[83] Studies have revealed that in this process, patients infected with SARS-CoV-2 have increased levels of multiple pro-inflammatory cytokines, including IL1β, IL2, IL6, IL10, interferon-γ (IFN-γ), tumor necrosis factor-α, IFN-γ-inducible protein 10, granulocyte-macrophage colony-stimulating factor, and monocyte chemoattractant protein-1.[82–85]

Obese individuals have upregulated pro-inflammatory genes: a systemic pro-inflammatory state extends to the pulmonary microenvironment, facilitating the occurrence of a cytokine storm.[86] Most pro-inflammatory adipokines, such as leptin, resistin, and osteopontin, are overproduced, while those with anti-inflammatory properties, such as adiponectin and ghrelin, are decreased.[87]

Nonetheless, elevated levels of leptin and the systematic increase in pro-inflammatory cytokines induce suppressor of cytokine signaling 1 and 3, which disables the leptin receptor and other cytokine receptors in immune cells, impairs early type I and III interferon responses, and disrupts the immune response.[88] By upregulating suppressor of cytokine signaling 1 and 3, SARS-CoV-2 adds a significant boost, which promotes a reactive delayed, but recurrent, immune response characterized by elevated inflammation states, such as the cytokine storm, endothelial damage, and hypercoagulation.[88]

For instance, in a study, lean and diet-induced obese mice were infected with the influenza A virus. Obese mice had significantly greater lung impairment and mortality rates, when compared to the lean controls. Furthermore, the mRNA production of antiviral and pro-inflammatory cytokines in the lungs of infected mice was markedly different between the two groups: INF-α and INF-β were minimally expressed in the infected lungs of obese mice, and there was a notable delay in the expression of pro-inflammatory cytokines IL6 and tumor necrosis factor-α. These results support the idea that genetic regulation in obesity may affect the immune response to viral infections.[89]

In the context of molecular genetics, GWAS have identified approximately 127 sites in the human genome, and the variants predispose to obesity.[90] Considering the inflammatory nature of this comorbidity, the hypothesis that variants in a number of these loci may also interfere with the pathogenesis of COVID-19 was listed, even independent of the development of obesity. However, further studies are needed to elucidate this gap.

Lung diseases

The existence of lung tissue damage, such as in chronic obstructive pulmonary disease, induces the increased expression of ACE2 in these tissues, thereby generating greater susceptibility to infection by SARS-CoV-2. This fact can be explained through several factors, such as increased transcription of the *ACE2* gene by stimulating sirtuin-1 (a class III histone deacetylase), and the modification of histones H3K27ac, H3K4me1 and H3K4me3, which are responsible for coordinating the transcription of genes associated with the *ACE2* gene. Furthermore, in lung diseases, ACE2 is overexpressed but is regulated by histone acetyltransferases and histone lysine deacetylases, from the attenuation of the chromatin structure, in addition to DNA hypomethylation, in the *ACE2* gene locus.[91,92]

It was also evident that the severity of COVID-19 correlates to the existence of previous pulmonary conditions of an individual. In this sense, studies have revealed that gene loci are associated with both lung diseases (such as interstitial lung disease, lung fibrosis, lung carcinomas, and decreased lung function) and the severity of SARS-CoV-2 infection. Such genes include *DPP9*, Forkhead box P4 protein (*FOXP4*), and surfactant protein D (*SFTPD*), in addition to mucin 5B (*MUC5B*). For example, in *FOXP4*, the increase in its expression is correlated to the increase in severity of COVID-19, and previous studies have reported this association in other diseases, such as lung cancer and interstitial lung diseases.[17,18,22]

Therefore, it is noteworthy that epigenetic mechanisms act on the expression of the ACE2 receptor, and consequently, on the greater susceptibility of individuals with lung diseases to SARS-CoV-2 infection, and that genetic variants associated with lung tissues and lung diseases can influence the severity of the disease.

Cardiovascular diseases, arterial hypertension and diabetes

The ACE2 receptor plays a fundamental role in controlling the Renin-Angiotensin System, and in vasodilation and blood pressure regulation through the degradation of Ang II into Ang 1–7.[91,93] Individuals with cardiovascular diseases have a higher expression of ACE2 receptors in tissues, and consequently, a greater susceptibility to infection by SARS-CoV-2. Hypertensive individuals suffer from DNA hypomethylation in CpG4 and CpG5 of the *ACE2* gene, and individuals undergoing drug therapy would present with a more significant expression of ACE2 to ensure homeostasis.[91,94]

Individuals with diabetes mellitus, especially type 2 diabetes mellitus, and diabetic nephropathy also present with a higher ex-

pression of ACE2 receptors. Drugs, such as ACE inhibitors and angiotensin receptor blockers, also favor this higher ACE2 expression. In addition to the greater susceptibility to infection by SARS-CoV-2 due to the higher expression of ACE2 receptors, the association of advanced glycemia with insulin resistance makes diabetic individuals more vulnerable to infection by the virus, and have greater risks of mortality. This fact can be explained by the cytokine storm that occurs in COVID-19, which results from the metabolic state of the diabetic individual, which in turn, leads to multiple organ failure.[91,95,96]

The exacerbated inflammatory response in severe COVID-19 is favored by the chronic inflammation promoted by diabetes, which affects glycemic regulation and peripheral insulin sensitivity, resulting in increased levels of IL6 and C-reactive protein. Thus, the pro-inflammatory state associated with diabetes favors the cytokine cascade, and exacerbates the inflammatory response associated with acute respiratory distress syndrome in individuals with COVID-19.[92,97] Therefore, individuals with chronic diseases, such as cardiovascular diseases, arterial hypertension, and diabetes, are more prone to SARS-CoV-2 infection and mortality.

Dyslipidemia

Studies have demonstrated the association of the *ApoE* gene with cholesterol homeostasis.[98–100] Through transporting cells with high cholesterol levels, ApoE promotes the greater entry of SARS-CoV-2 into the human body, and the greater infectivity by the virus. Cholesterol plays an important role in the regulation of COVID-19 infection, given that the lipid environment helps in the entry of the virus through endocytosis into the host cell, and this is associated with the availability of the receptor for high-density lipoprotein scavenger class B type 1. In addition, cholesterol is simultaneously transported to the site of endocytosis with ACE2, and the lipid environment would favor the presence of ACE2 receptors for the virus S protein in the microdomains of the plasmatic membrane.[101–104]

Therefore, cholesterol is associated with increased susceptibility to SARS-CoV-2 infection. In this sense, environmental factors, such as age, smoking and high-fat diet, in addition to the presence of chronic diseases, are closely correlated to the greater susceptibility to COVID-19 infection. Furthermore, the relationship of these factors with higher serum cholesterol levels in the host should not be ignored, and this be considered as a potential mechanism of association between these environmental factors and the severity of COVID-19.[101,102,105,106] However, further studies are required to determine the exact role of cholesterol-transporting lipoproteins associated with virus infection.

Conclusions and future perspectives

A number of genetic and epigenetic variants have been associated with the susceptibility and severity of COVID-19. Thus, knowledge of host genetics is essential for elucidating the biological mechanisms underlying the patterns of susceptibility and prognosis of infectious diseases. In the case of COVID-19, which is a disease with a significant global impact, this understanding may guide studies and the development of tools, such as polygenic risk scores and new medications, in order to define better behaviors for more individualized and adequate management.

Acknowledgments

None to declare.

Funding

This research received no specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

BFK and PRB: study concept and design; BFK, IPSC, RCP and PRB: drafting of the manuscript; RCP and PRB: critical revision of the manuscript for important intellectual content; PRB: study supervision. All authors have significantly contributed to the study, and approved the final manuscript.

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