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# Host polymorphisms and COVID-19 infection

Joris R. Delanghe<sup>a,\*</sup> and Marijn M. Speeckaert<sup>b,c</sup>

<sup>a</sup>Department of Diagnostic Sciences, Ghent University, Ghent, Belgium

<sup>b</sup>Department of Nephrology, Ghent University Hospital, Ghent, Belgium

<sup>c</sup>Research Foundation-Flanders (FWO), Brussels, Belgium

\*Corresponding author: e-mail address: joris.delanghe@ugent.be

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## Abstract

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). There is growing evidence that host genetics play an important role in COVID-19 severity.

Based on current knowledge about the human protein machinery for SARS-CoV-2 entry, the host innate immune response, and virus-host interactions, the potential effects of human genetic polymorphisms, which may contribute to clinical differences in SARS-CoV-2 pathogenesis, may help to determine the individual risk for COVID-19 infection and outcome.



## 1. Introduction

The outbreak of the COVID-19 pandemic shows a marked geographical variation in its prevalence and mortality. The question arises if the geographical variation of human polymorphisms may affect the prevalence and the mortality of COVID-19. In this review, we will give an overview of several candidate genes that may play a role in the immune defense against COVID-19.



## 2. Genetic polymorphisms affecting the angiotensin-converting enzyme 2 expression (Table 1)

### 2.1 Angiotensin-converting enzyme 2

The angiotensin-converting enzyme 2 (*ACE2*) gene is composed of 18 or 19 exons (v1 and v2), spanning approximately 40 kb of genomic DNA on the human X-chromosome, that encode the same protein (805 amino acids)

**Table 1** Genetic polymorphisms affecting the ACE2 expression

	Potential underlying working mechanisms	References
ACE2	ACE2 acts as a receptor molecule for SARS-CoV-2.	[1]
TMPRSS2	TMPRSS2 allows fusion of the viral and host cell membranes, playing an important role in the initial phase of the SARS-CoV-2 infection.	[2,3]
AR	AR mediates transcriptional regulation of ACE2 and TMPRSS2 expression.	[4]
ADAM17	ADAM17 stimulates ACE2 shedding into the extracellular cellular space.	[5]
ACE1	ACE1 deletion allele is associated with a reduced expression of ACE2.	[6]

ACE, angiotensin-converting enzyme; ADAM17, a disintegrin and metalloproteinase 17; AR, androgen receptor; TMPRSS2, transmembrane serine protease 2.

and three other smaller variants: x1, x2, and x3. It is a homolog of the ACE1 protein and has 40% identity of amino acid sequence to its N- and C-terminal domains [7,8]. The *ACE2* gene encodes a zinc metalloprotease, which acts as a receptor molecule for three strains of coronavirus, severe acute respiratory syndrome-associated coronavirus (SARS-CoV), NL63, and recently SARS-CoV-2 [1]. ACE2 is expressed in almost all human organs more or less [9], e.g., in a normal adult human lung, alveolar epithelial type II cells are the primary expression site of ACE2 [10]. 1700 *ACE2* variants have been identified in the ChinaMAP and 1KGP databases, whereas 25 different *ACE2* gene variants are included in the Leiden Open Variation Database [11]. Several of these *ACE2* SNPs have been linked to the prevalence and outcome of COVID-19.

Specific genetic variations in the ACE2 sequence may influence the cell-entry efficiency of viruses, either by changing its expression levels or causing a higher binding affinity for SARS-CoV-2. In silico analysis showed that rs233574, rs2074192, and rs4646188 may significantly alter the RNA secondary structure. These SNPs may dysregulate the ACE2 transcription/translation or its protein stability, resulting in changing the binding of SARS-CoV-2 to the ACE2 receptor and modulating COVID-19 pathogenesis [12]. The rs233574 distribution in Asians is significantly different compared with other populations, with a predominance of the T allele vs. the C allele [13]. In the presence of the T allele, the rs233574 sequence can bind to the ETR-3 splicing factor, increasing the susceptibility for COVID-19. It was suggested that 9 other *ACE2* SNPs may affect the splicing factor binding affinity [12]. Genetic variations in *ACE2* may affect its function and structure, and alter the recognition by SARS-CoV-2. More in detail, the binding of the catalytic metal atom to decrease ACE2 activity could be weakened by p.His378Arg, whereas p.Ser19Pro could distort the most important helix to the S-protein. Secondary structures could be affected by 7 other missense variants (i.e., p.Arg219Cys, p.Arg219His, p.Asp206Gly, p.Gly211Arg, p.Ile468Val, p.Lys341Arg, and p.Ser547Cys), whereas p.Ile468Val is only present in Asian populations [14].

Large variations in calculated binding energy in different ACE2 variants towards SARSCoV-2S protein have been reported. The calculated binding energies can be ranked from high to low with the corresponding population with the highest allele frequency: G211R (European, South Asian), D206G (European), K341R (African, African American), R219C (South Asian), I468V (East Asian), K26R (Ashkenazi Jews). These findings give indications regarding the populations that could be more prone to SARS-CoV-2

infection due to enhanced binding affinity [15]. Molecular dynamic demonstrated that I468V and K26R may affect binding characteristics between the S protein of the virus and the human ACE2 receptor [16]. Besides K26R, a specific SNP (S331F) was identified in the Iranian population, which could reduce the receptor affinity for the viral Spike protein [17]. DOCK and FireDock simulations identified 6 *ACE2* missense variants (A25T, E37K, E75G, I21T, K26R, T55A) with higher affinity for SARS-CoV-2 Spike protein receptor-binding domain for wild type ACE2, and 11 variants (E23K, E35K, I21V, K26E, K68E, M82I, N51D, N58H, S43R, T27A, Y50F) with a lower affinity [18]. An *in-silico* study showed that mutations W461R, G405E and F588S in ACE2 receptor protein and population-specific mutations P391S, C12S, and G1223A in the spike glycoprotein were predicted as highly destabilizing to the structure of the bound complex [19].

Whole-exome sequencing data of 6930 Italian control individuals identified three variants [c.2158A > G p.Asn720Asp, c.1166C > A p.Pro389His, and c.1051C > G p.Leu351Val] that may interfere with protein structure and stabilization. These polymorphisms are moderately expressed in the Italian and European non-Finnish populations and with a very low allele frequency or not occurring in the Eastern Asia population. Besides, p.Leu351Val and p.Pro389His are rare variants likely interfering with the internalization process. A statistically significant higher allelic variability was observed in controls ( $n = 258$ ) compared with patients ( $n = 131$ ) [20]. In a cohort of Russian COVID-19 patients, several rare ACE2 variants (including rs146598386, rs73195521, rs755766792, and others) were likely to predispose to severe COVID-19 infection and may account for certain (though not the majority of) severe COVID-19 cases [21]. Two particular ACE2 alleles, including rs143936383 and rs73635825 (which is common in Africans), demonstrated a relatively reduced binding affinity for the viral spike protein, indicating a reduced likelihood of SARS-CoV-2 attachment and possible lowered susceptibility to infection [22].

Exploring the allele frequency distribution of 1700 variants in the *ACE2* gene among different worldwide populations, 11 common variants and one rare variant were associated with enhanced ACE2 expression. There was an uneven distribution among different populations. In the East-Asian population, a specific *ACE2* gene polymorphism (variant rs4646127) was strongly associated with higher ACE2 expression concentrations [23]. Two specific ACE2 alleles (rs73635825 and rs143936283) exhibited a relatively low binding affinity and lack of some of the key residues in the complex formation

with SARS-CoV-2 spike protein, which might imply a lower likelihood of viral attachment and potential resistance to infection [1]. Two other ACE2 variants have been associated with an increased risk of being susceptible to SARS-CoV-2: the minor A allele in the rs2106806 variant (OR 3.75) and the minor T allele in the rs6629110 variant (OR 3.39) [24]. In British individuals, SNP rs2074192 was nominally significantly associated with more severe outcomes of COVID-19 within obese smoking males of 50 years or older [25].

Analysis of the data from the 1000 Genomes Phase 3 database (1000G), which comprises 84.4 million variants in 2504 individuals from 26 different populations, showed an absence of relevant polymorphisms of the *ACE2* gene related to the protein binding region to the viral particle as many of those located in coding regions have minor allele frequencies (MAFs) close to or less than 0.001, as well as a very low possibility of conferring any global (or population) impact on the destination of the disease. Fifteen SNPs with the potential to cause changes in the protein structure of ACE2 that may impact virus-cell interactions have been identified, but are restricted to specific populations, which may have some clinical-epidemiological consequences in some regions compared to others in the world. The rs182366225 and rs2097723 polymorphisms that potentially may increase the expression of the ACE2 are more frequent in the East Asian population (even higher in Chinese and Vietnamese populations). Exclusive genetic polymorphisms (rs1027571965 and rs889263894) or higher frequencies (rs2285666 and rs35803318) are observed in the indigenous populations from Amazon in comparison with other populations [26]. These polymorphisms are related to increased expression of the *ACE2* gene in brain tissues, among others [27]. Higher rates of three relevant polymorphisms (rs147311723, rs142017934, and rs4646140) are observed among African populations with an exclusive polymorphism in rs142017934, which can influence the translation regulation of the *ACE2* gene. Besides, a higher frequency of rs5934250 that seems to reduce the expression of ACE2 in some tissues has been found in Europeans and some Africans [26].

Furthermore, the polymorphism rs2285666 (also called G8790A) varies significantly among Europeans (0.235), Americans (0.336), Africans (0.2114) and Asians (0.55) [23,28]. In the Indian population, a mean frequency  $\sim 0.6$  of this allele has been reported [29]. The alternate allele (TT-plus strand or AA-minus strand) of rs2285666 is associated with an increased expression up to 50% of the *ACE2* gene and may play a role in SARS-CoV-2 susceptibility [28]. A strong correlation of alternate allele

(allele T on the plus strand or allele A on the minus strand) of variant rs2285666 with a lower infection rate as well as a lower case fatality ratio among Indian populations has been demonstrated [29]. As rs2285666 is a potential risk factor for type 2 diabetes, hypertension, and coronary artery disease [28], this SNP may be associated with the comorbidities observed in COVID-19 patients [29]. In contrast to the previous findings, no association between ACE2 rs2285666 polymorphism and COVID-19 outcome has been documented in a Spanish case-control study [30].

Other reports did not show an association between ACE2 genotypes and COVID-19 [31].

## 2.2 Transmembrane serine protease 2

Transmembrane serine protease 2 (TMPRSS2) is a serine protease, which allows fusion of the viral and host cell membranes, playing an important role in the initial phase of the SARS-CoV-2 infection. TMPRSS2 is highly expressed in the human respiratory system and decreases with age [2,3]. A significantly higher expression of TMPRSS2 is found in androgen-sensitive tissues (prostate and testis), making males more vulnerable for the acquisition of infection [32]. The *TMPRSS2* gene is located on chromosome 21q22.321 [33] and is a highly polymorphic gene. Four regulatory SNPs from TMPRSS2 (rs112657409, rs11910678, rs77675406 and rs713400) have significant role in regulation of expression of TMPRSS2 [34]. The TMPRSS2 rs12329760 polymorphism corresponds with the exonic splicing enhancer srp40 site, and a variant allele of rs12329760 polymorphism could increase the chance of faulty expression due to potential disruption of the exonic splicing enhancer site [35]. rs12329760 is 15% more frequent in populations of East Asia (38%) than in European populations (23%) [36]. Several studies have linked TMPRSS2 DNA polymorphisms with COVID-19 susceptibility, severity, and clinical outcomes. Unique but prevalent polymorphisms in TMPRSS2, including the one that procures an amino acid change (Val160Met) (rs12329760), may provide potential explanations for differential genetic susceptibility to COVID19 as well as for risk factors, including cancer and the high-risk group of male patients [37]. The missense substitution in Val160Met affects a residue away from the serine protease catalytic triad and does not affect any post-translational modification [38,39]. After performing performed an in-depth genetic analysis of chromosome 21, GWAS data of a cohort of 908,494 subjects with European origins from the COVID-19 Host Genetics Initiative identified

five common variants (rs3787946, rs9983330, rs12329760, rs2298661, and rs9985159) at locus 21q22.3 within *TMPRSS2* and near the *MX1* gene that showed suggestive associations with severe COVID-19. In comparison with control subjects, the alleles with minor frequency were less recurrent among hospitalized patients, suggesting their protective role against the progression of the disease. In two cohorts of Asian origin, all five SNPs were replicated, whereas two SNPs were replicated in a case series of African ancestry. The minor allele of four of the top five SNPs might reduce the expression of *TMPRSS2* in lung tissues. The rs12329760 SNP, in addition to its eQTL role, decreased the stability of the protein and ACE2 binding, which might impede viral entry [40]. In silico analysis showed the creation of a de novo pocket protein associated with this variant [41]. Using data of the 1000 Genome Project and web-based tools, 17 *TMPRSS2* polymorphisms generated a possible functional effect: the binding of different transcription factors and microRNAs. The minor allele frequencies of these polymorphisms vary in each community with higher frequencies in specific populations [39].

In another study, rs469390, rs2070788, rs77675406, and rs464397 were associated with differential expression of *TMPRSS2*. rs469390 encodes a missense mutation with the highest pulmonary *TMPRSS2* expression in AA carriers, an intermediate expression heterozygous AG carriers showing intermediate expression, and the lowest expression in the homozygous GG genotype. A higher *TMPRSS2* expression may be associated with a higher susceptibility for COVID-19. Besides, the highest *TMPRSS2* expression in the lung was observed in rs464397 and rs383510 homozygous TT genotypes, in comparison with the intermediate and low expression in heterozygous CT and homozygous CC genotypes, respectively. Considering the rs2070788, the pulmonary *TMPRSS2* expression was higher in individuals with GG genotype than in the heterozygous AG and AA genotypes. Overall, the frequencies of variant alleles [rs464397 (T allele), rs469390 (A allele), rs2070788 (G allele), and rs383510 (T allele)] associated with a high pulmonary *TMPRSS2* expression seemed to be higher in European, African, and American populations than in East Asian populations, which might lead to higher susceptibility to COVID-19 [2]. However, other reports show extremely lower frequencies of SARS-CoV-1 susceptibility alleles in Africans, reaching to 32-fold decrease compared to other populations [42,43]. The haplotype, characterized by 3 SNPs (rs2070788, rs9974589, rs7364083), is also associated with a higher *TMPRSS2* expression and is significantly increased in Europeans in comparison with East



Asians [28]. Other TMPRSS2 SNPs, which might be associated with an increased risk/susceptibility for COVID-19 are rs4818239, rs62217531, rs75603675, rs2298662, and rs997499 [44].

### 2.3 Androgen receptor

In human prostate and lung cells, evidence for the androgen receptor (AR)-mediated transcriptional regulation of TMPRSS2 and ACE2 expression has been provided [4]. The AR contains in its N-terminus domain a polymorphic polyQ tract, ranging between 9 and 36 repeated glutamine residues in the normal population [45]. The AR polyQ length correlates with receptor functionality. Shorter polymorphic glutamine repeats are typically associated with higher and longer PolyQ tracts with lower receptor activity [46]. A variation of the allele distribution of the PolyQ repeat length is observed among different populations, with the longest in Asians, medium in Caucasians, and shortest in Africans [47]. Shorter polyQ alleles ( $\leq 22$ ) in the androgen receptor (AR) showed protection against severe outcomes in COVID-19. Among carriers of the long-polyQ alleles, inappropriately low serum testosterone concentrations predicted the need for intensive care in COVID-19 infected men [48].

### 2.4 A disintegrin and metalloproteinase 17

ADAM 17 (a disintegrin and metalloproteinase 17) is a protein involved in the shedding of several membrane proteins, which are important for inflammation and immunity [tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), intercellular adhesion molecule-1 (ICAM-1), and ACE2] [49]. An increased expression and activity of ADAM17 are seen in patients with sepsis. The *ADAM17* locus on chromosome 2p25.1 consists of two clusters. Three unique SNPs have been identified that induce strong differences in terms of allelic profiles between European and Asian populations. Direct action of ADAM17 on ACE2 has been demonstrated, leading to ACE2 shedding into the extracellular cellular space. As TMPRSS2 cleaves not only ACE2, but also the S protein of SARS-CoV-2 leading to membrane fusion and cellular uptake of the virus, ADAM17 and TMPRSS2 may have opposite effects on net ACE2 shedding. There is a strong possibility that genetic polymorphisms influencing ADAM17 expression also contribute to the modulation of ACE2 shedding intensity in COVID-19 [5].

## 2.5 Angiotensin-converting enzyme 1

The human *ACE1* gene, located at chromosome 17, is characterized by an insertion (I) or deletion (D) of a 287 base pair (bp) Alu repeat sequence in intron 16. Three different genotypes (ACE1 II, ID and DD) have been identified, represented by four individual SNPs (rs4646994, rs1799752, rs4340 and rs13447447) [50,51]. A worldwide geographic genetic analysis showed a decline of the D-allele from the highest frequency in African and Arab regions (0.57–0.88), intermediate frequencies in Europe, Australia, and America, and the lowest frequency in East-Asia (0.12–0.27) [52]. Significantly higher serum ACE1 concentrations are found in subjects with the DD genotype compared with those with either the ID or II genotypes [53].

Next to the ACE2 polymorphism, also the ACE1 I/D polymorphism may be regarded as a confounder in the spread of COVID-19 and the outcome of the infection. ACE2 counteracts the effects of its homolog ACE1. As ACE1 and ACE2 levels are regulated by common genetic variants in their genes [54], ACE2 concentrations are also influenced by this polymorphism. The D/I polymorphism in the *ACE1* gene contributes to the variation in alveolar protein expression of ACE2 [55]. On a population level, the log-transformed prevalence of and mortality due to COVID-19 in 33 countries (on April 1, 2020), negatively correlated with the ACE D allele frequency [6]. However, in another population study with different countries, an increased frequency of the ACE1 II genotype was inversely correlated with susceptibility to SARS-CoV-2 infection and consequent mortality [56]. Severe COVID-19 was also associated with the ACE1 D/D genotype in Spanish patients [30], and the D allele D of ACE I/D polymorphism is associated with the rate of infection and mortality in the Asian population [57]. The deletion is associated with a reduced expression of ACE2 [6]. Viral infection may lead to further suppression of ACE2 function and cause ACE1/ACE2 imbalance responsible for RAAS over-activation and pulmonary shutdown [54]. The ACE1/ACE2 imbalance predicts that COVID-19 patients with the D allele of ACE1, especially the DD genotype, will have a more severe course of the disease, as seen in SARS patients with an ACE1 DD genotype [58,59]. An Italian study showed an inverse correlation between the I/I polymorphism and COVID-19-related deaths [60], whereas others investigated the link between ACE I/D polymorphism and acute pulmonary embolism in COVID-19 pneumonia. The prevalence of D/D homozygous polymorphism was significantly higher in COVID-19

patients with a pulmonary embolism in comparison with those without pulmonary embolism, while heterozygote I/D polymorphism was significantly lower expressed in the group with pulmonary embolism in comparison with the group without pulmonary embolism [61]. In a meta-analysis with 48,758 healthy subjects from 30 different countries, it was also demonstrated that a higher I/D ratio was associated with a significantly increased recovery rate, but not with death rate [62]. The contradictory results could be explained by a different genetic background, geographic and ethnic differences between populations, demographic characteristics of the population (gender, age), comorbidities, lifestyle, social and public health factors.



### **3. Genetic polymorphisms affecting the immune response against COVID-19 (Table 2)**

#### **3.1 C—C chemokine receptor 5**

C—C chemokine receptor 5 (CCR5) is a member of the G protein-coupled receptor family abundantly present on the surface of monocytes, T cells, and macrophages. CCR5 induces inflammation in a wide range of infectious diseases and recruit leukocytes towards inflammation sites [72]. Differential surface expression of CCR5 has been linked with susceptibility/resistance in a wide range of viral diseases. The *CCR5* gene is located at the short arm (p.21) of chromosome 3. A common 32bp deletion variant at the coding region leads to the creation of a premature stop codon and a shorter amino acid length. CCR5  $\Delta 32$  variant produces a truncated protein and significantly diminishes surface expression of the receptor [73]. In European populations, the CCR5- $\Delta 32$  mutation is highly prevalent with an average frequency of 10%, showing a strong geographic north-to-south cline with the highest frequencies in Nordic countries and the lowest in Southern European populations [74]. On a population level, a positive correlation was observed between COVID-19 infection and mortality rate, and the frequency of the CCR5  $\Delta 32$  allele. In an African population, the CCR5  $\Delta 32$  minor allele frequency correlated positively with the COVID-19 mortality rate. Differential expression of chemokine receptor and ligand may contribute to variations in inflammatory pattern, although the exact underlying working mechanism of the CCR5  $\Delta 32$  allele with the increased susceptibility for SARS-CoV-2 infection and death is not yet known [63]. However, these findings could not be confirmed in other studies [74,75].

**Table 2** Genetic polymorphisms affecting the immune response

	<b>Potential underlying working mechanisms</b>	<b>References</b>
CCR5	CCR5 may contribute to variations in inflammatory pattern, although the exact underlying working mechanism of the CCR5 $\Delta$ 32 allele with the increased susceptibility for SARS-CoV-2 infection and death is not yet known.	[63]
Complement C3	Complement C3 stimulates effective clearance of excessive binding of leukocytes to the vascular wall by complements.	[64]
IFITM3	IFITM3 is involved in the antiviral defense in the adaptive and innate immune response, preventing hemifusion of the viral membrane and host cellular membrane in SARS-CoV.	[65]
TNF- $\alpha$	TNF- $\alpha$ is a central element in the host defense response.	[66]
TLR7	TLR7 is a crucial components in the initiation of innate immune responses to a variety of pathogens, causing the production of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, and IL-6) and type I and II Interferons (IFNs), which are responsible for innate antiviral responses.	[67]
ApoE	ApoE e4 not only affects lipoprotein function, but also moderates macrophage pro-/anti-inflammatory phenotypes.	[68]
DBP	Besides the potential protective effects of vitamin D, DBP is involved in actin scavenging, macrophage activation, enhancement of the leukocyte chemotactic activity of activated complement peptides, and fatty acid transport.	[69]
DPP4	DPP4 activity differentially regulates glucose homeostasis and inflammation.	[70]
GSTT1	GSTT1 is involved in the cellular detoxification process.	[71]

CCR5, C—C Chemokine Receptor 5; IFITM3, interferon-induced transmembrane 3; TNF- $\alpha$ , tumor necrosis factor-alpha; TLR7, Toll-like receptor 7; ApoE, apolipoprotein E; DBP, vitamin D binding protein; DPP4, dipeptidyl peptidase-4, GSTT1, glutathione S-transferase theta 1.

### 3.2 Complement C3

Complement factor 3 (C3), a large molecular weight protein (185 kDa), is a central component of the innate immune system, which forms in association with other complement proteins, a major host mechanism for detection and clearance of potential pathogens [76]. The C3 polymorphism is defined by two allelic variants [S (slow) and F (fast)], based on the differential mobility on high voltage agarose gel electrophoresis of the resulting proteins in serum [77], leading to three phenotypes (C3SS, C3FS, and C3FF) [78]. The molecular difference between C3S and C3F [amino acid substitution R-G at nucleotide position 394 (C-G)] is determined by SNP rs2230199 [79]. The allelic frequency of C3F is lowest among Asians (1%), intermediate among blacks (5%), and highest among whites (20%). The C3 polymorphism, a representative of the first principal component of European gene frequencies, may be regarded as a confounder in the spread and outcome of COVID-19. More in detail, the C3S allele frequency showed a negative correlation with COVID-19 prevalence and outcome in a multivariate model [6]. The observed association between C3 polymorphism and COVID-19 could be explained by the effective clearance of excessive binding of leukocytes to the vascular wall by complements, especially C3 [64].

### 3.3 Interferon-induced transmembrane protein 3

The interferon-induced transmembrane (IFITM) proteins are involved in the antiviral defense in the adaptive and innate immune response, preventing hemifusion of the viral membrane and host cellular membrane in a broad spectrum of enveloped viruses, e.g., SARS-CoV [65]. An upregulation of IFITM3 is explicitly observed in SARS-CoV-2 infected lung epithelial cells and the lung tissue-resident memory CD8<sup>+</sup> T-cells [65,80]. The human *IFITM* locus is located on chromosome 11p15.5 and consists of five genes, including IFITM3. The *IFITM3* gene is an IFN-stimulated gene (ISG) and the protein IFITM3 is mainly expressed on endosomes and lysosomes [81]. IFITM3 SNPs may diminish the antiviral effects of IFITM3 causing a higher infection susceptibility and disease severity. In comparison with East Asians, the C-allele of rs12252, which is located on the splicing receptor, is less common in Europeans, with a minor allele frequency (MAF) of 0.04, in comparison with 0.47 [82]. In a small preliminary study in the Han Chinese population, a significantly higher frequency of rs12252 C-allele carriers in patients with severe COVID-19 ( $n = 24$ ) was observed compared to patients with mild COVID-19 ( $n = 56$ ) [83]. A higher risk for SARS-CoV-2

infection was found in rs12252 C-allele carriers than in the reference group [83,84]. A worldwide epidemiological investigation confirmed the significant association of the rs12252-CC genotype with severe COVID-19 [85].

However, in a German cohort study, no association between IFITM3 rs12252 and SARS-CoV-2 infection susceptibility or COVID-19 severity was found. The A-allele of a second SNP (rs34481144, c.-22-64G > A) has the highest MAF in Europeans (0.46) and a very low MAF in East Asians [86]. The A allele of this promoter SNP shows decreased IFITM3 mRNA and protein levels, diminishing the antiviral defense capacities of IFITM3 [87]. In a case-control study in Caucasians, there was no difference in the frequency of rs34481144 alleles or genotypes in SARS-CoV-2-positive ( $n = 239$ ) compared to SARS-CoV-2-negative ( $n = 239$ ) patients [86]. In contrast to the previous finding, a significant correlation and a striking agreement was observed between the reported standardized mortality ratios and the frequency of the combined haplotype of rs12252 and rs34481144 of ethnic groups in England. At population level, the allele frequency of the rs6598045 SNP of the *IFITM3* gene, which is located on the proximal promoter of the *IFITM3* gene, strongly correlated with the case fatality rate of COVID-19 [88]. This SNP is related to transcriptional efficiency via the binding ability of the transcription factor TFII-I [89]. Additional studies are needed to clarify the influence of the different IFITM3 SNPs on SARS-CoV-2 infection risk and the course of COVID-19 [90].

### 3.4 Tumor necrosis factor-alpha

Tumor necrosis factor-alpha (TNF- $\alpha$ ) is a central element in the host defense response [66]. Patients with COVID-19 infection have much higher serum TNF- $\alpha$  concentrations, which are positively correlated with the severity of the disease [91]. Several TNF- $\alpha$  polymorphisms have been detected inside the TNF- $\alpha$  promoter at the positions, relative to the transcription start site, -1031 (T/C), -308 (G/A), -238 (G/A), -851 (C/T), -857 (C/A), -863 (C/A), -419 (G/C), -49 (G/A), -376 (G/A), and -162 (G/A) [92]. The gene distribution of TNF- $\alpha$  may be an independent factor in the control of the severity and prognosis of COVID-19. Individuals carrying the A allele (AA and GA) are more susceptible to the disease. Analyzing the severe cases of SARS-CoV-2 infections showed a high percentage (80%) in the AA genotype, an intermediate one (41.7%) in patients with a GA genotype and no cases in the GG genotype group.

The AA genotype was also associated with a poor prognosis in comparison with the other genotypes. These findings may be related to variations in serum TNF- $\alpha$  levels with a high TNF- $\alpha$  production in A allele carriers [66].

### 3.5 Toll-like receptor 7

Toll-like receptors (TLRs) are crucial components in the initiation of innate immune responses to a variety of pathogens, causing the production of pro-inflammatory cytokines (TNF- $\alpha$ , IL-1, and IL-6) and type I and II Interferons (IFNs), which are responsible for innate antiviral responses [67]. TLR7 recognizes several single-stranded RNA viruses including SARS-CoV-2 [93]. Exploring the presence of genetic variants associated with primary immunodeficiencies among young patients with COVID-19, van der Made et al. demonstrated the presence of rare putative loss-of-function variants of X-chromosomal TLR7 in a case series of 4 young male patients [94]. In a nested case-control study, the X-chromosomal TLR7 loss-of-function variants were confirmed in 2% of severely affected young males (less than 60 years old) and in none of the asymptomatic participants. A reduced TLR7-related gene expression will lead to impaired type I and II IFN responses [67]. As some of the rare TLR7 variants will only have a marginal effect on the release of type I interferon, additional pathways will influence the body's defense against SARS-CoV-2 infection [67].

### 3.6 Apolipoprotein E

The human apolipoprotein E (*ApoE*) gene is characterized by 3 major polymorphic alleles ( $\epsilon$ 2,  $\epsilon$ 3, and  $\epsilon$ 4), which have an allele frequency of 8.4%, 77.9%, and 13.7%, respectively, in the general population [95]. The 3 ApoE protein isoforms (E2, E3, and E4) [96] have markedly different effects on lipid metabolism [97]. In the UK Biobank Community Cohort study from genetically European ancestry participants, and type-2 diabetes, the ApoE  $\epsilon$ 4 allele is associated with an increased risk of severe COVID-19 infection, independent of preexisting dementia, cardiovascular disease, and type-2 diabetes. ApoE  $\epsilon$ 4 $\epsilon$ 4 homozygotes were more likely to be COVID-19 test positives compared to  $\epsilon$ 3 $\epsilon$ 3 homozygotes [98]. These data were confirmed in a Spanish cohort of old people [99]. ApoE4 is also associated with increased SARS-CoV-2 susceptibility in both neurons and astrocytes [95]. ApoE4 may lead to metabolic deregulation, manifested by elevated cholesterol and oxidized lipoprotein concentrations. This may increase the susceptibility of pneumocytes to SARS-CoV-2 infection and

may exaggerate pulmonary inflammation [100]. ApoE e4 not only affects lipoprotein function (and subsequent cardio-metabolic diseases), but also moderates macrophage pro-/anti-inflammatory phenotypes [68]. Besides ACE2, ApoE is one of the highly co-expressed genes in type II alveolar cells in the lungs [101].

### 3.7 Vitamin D binding protein

Vitamin D binding protein (DBP) or “group-specific component” (Gc) is a 52–59 kDa serum  $\alpha_2$ -globulin showing a considerable polymorphism in humans. The human *DBP* gene is localized at 4q11–q13 on chromosome 4. Three common alleles have been identified with faster and slower migration rates: DBP1F (fast), DBP1S (slow), and DBP2 [102]. Parker et al. have published a simple classification system of DBP-phenotypes according to this electrophoretic technique: DBP1-1 (DBP1F-1F, DBP1F-1S, and DBP1S-1S), DBP2-1 (DBP2-1F and DBP2-1S), and DBP2-2 (DBP2-2) [102]. The three major circulating DBP alleles are defined by the genetic polymorphisms rs7041 and rs4588: DBP1F [rs7041-T (ASP), rs4588-C (Thr)], DBP1S [rs7041-G (ASP), rs4588-C (Thr)], and DBP2 [rs7041-T (ASP), rs4588-A (Lys)] [103].

The potential role of vitamin D and vitamin D-related gene polymorphisms in the prevention and treatment of patients with a SARS-CoV-2 infection is still a matter of debate. Comparing the frequency of the DBP1 allele in 55 countries with the prevalence and mortality data of COVID-19, taking into account the time interval since the start of the infection in each country, showed a potential protective effect of DBP1-carriers [104]. This finding could be partly explained by the protective effects of vitamin D as in healthy, white, premenopausal women, the median plasma 25-OH vitamin D and 1,25-OH vitamin D concentrations were highest in the DBP1-1 group, intermediate in the DBP2-1 group, and lowest in the DBP2-2 group [69]. Under physiological conditions, DBP binds nearly all (85–90%) circulating vitamin D, whereas only 10–15% is associated with albumin, and <1% is present in its free form [105]. The 5-fold difference in the mean serum DBP concentration among the 3 common DBP phenotypes (with the highest level in DBP1-1 subjects and the lowest in DBP2-2 individuals), might also partly explain the lower COVID-19 risk of DBP1 carriers. Apart from its specific sterol binding capacity, DBP exerts several other important biological functions which could play a role in different clinical stages of COVID-19, such as actin scavenging, macrophage activation,



enhancement of the leukocyte chemotactic activity of activated complement peptides, and fatty acid transport [105]. Besides, Batur et al. observed a positive association between TT and GT genotypes at rs7041 locus and the COVID-19 prevalence and mortality [106].

### 3.8 Dipeptidyl peptidase

Dipeptidyl peptidase-4 (DPP4) or CD26 is an exopeptidase, that participates in various physiological processes and is present in two forms (anchored to the cell membrane or soluble, circulating in plasma) [107]. This serine peptidase is expressed in endothelial, bronchiolar epithelial, alveolar epithelial, and blood cells (particularly lymphocytes) [108,109]. In silico prediction has suggested the intermolecular interactions between SARS-CoV-2 surface spike protein (S) and the receptors TMPRSS2 and CD26 [34]. Via its enzymatic activity and non-enzymatic immunomodulatory effects, DPP4 activity differentially regulates glucose homeostasis and inflammation. DPP4 is a co-stimulator for T cell activation by binding to adenosine deaminase (ADA), whereas it also enhances lymphocyte proliferation independent of ADA binding [70]. Studies on the genetic susceptibility of CD26 for COVID-19 showed a correlation between rs13015258 missense variant in the *CD26* gene and the susceptibility to SARS-CoV-2 infection. This SNP is not located within the receptor-ligand (S1 domain of SARS-CoV-2) binding site. CD26 overexpression by epigenetic modification at rs13015258-C allele could explain the higher SARS-CoV-2 infected fatality rate among type 2 diabetes [34]. Besides, the rs3788979 *DPP4* polymorphism has been associated with a high risk of COVID-19. Individuals with rs3788979 TT genotype might produce low levels of DPP4, being more susceptible to infection and progression of the disease [110]. However, in a preliminary Italian cohort study, no difference in the frequency of the variants of the *DPP4* gene, compared to those reported in the GnomAD database, was found [111]. In a GWA study of COVID-19 patients from the UK, rs2109069 located in the *DPP9* gene was one of three polymorphisms associated with severe COVID-19 [112]. DPP9 and DPP4 are members of the S9B subfamily of peptidases with a high structural resemblance. DPP9 is expressed in leukocytes, activated lymphocytes, lymphocytes infiltrating inflamed lungs, and bronchi after induction of experimental asthma, and participates in the immune and inflammatory processes [110].

### 3.9 Glutathione S-transferase theta 1

The glutathione S-transferase theta 1 (GSTT1, MIM: 600436) belongs to the glutathione S-transferases (GSTs) superfamily, involved in catalyzing the conjugation reactions of reactive intermediates of electrophilic compounds with cytosolic glutathione. In contrast to GSTM1 (GSTM1, MIM: 138350), a higher expression of GSTT1 in the lung tissue has been demonstrated. The *GSTT1* gene is characterized by a deletion polymorphism, and these *GSTT1* null genotypes have been associated with an increased risk of several oxidative stress-associated multifactorial diseases [113]. In comparison with East-Asian populations, European populations show a lower frequency of the *GSTT1* null genotype. Countries with a lower frequency of the *GSTT1* null genotype show higher mortality and case-fatality due to SARS-CoV-2 infection, but are not associated with an increased prevalence of COVID-19. In this way, the null genotype of *GSTT1* may be regarded as a predictor for mortality and case-fatality of COVID-19. This association with COVID-19 outcome, but not with the prevalence of COVID-19, might be explained by the fact that GSTT1 is involved in the cellular detoxification process [71].



## 4. Associated genetic polymorphisms (Table 3)

### 4.1 ABO blood group

The *ABO* gene, located on the 9th chromosome, consists of 7 exons and codes for enzyme glycosyltransferases, which are responsible for the formation of antigens in blood type A and/or B [120]. Driven by the associations between blood group and other infections, including SARS-CoV-1 [121–123] for which was demonstrated that individuals with blood type O were less likely to become infected with SARS compared with non-blood type O individuals [121], several studies have also suggested an association between ABO blood group types and the risk of COVID-19 infection and outcome. Although there is no consensus yet, most researchers have reported an increased risk of infection and mortality in individuals with blood group A [124–127]. In a genome-wide association study involving 1980 patients with COVID-19 and severe disease, a 3p21.31 gene cluster (spanning the genes *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*) was identified as a genetic susceptibility locus in COVID-19 patients with respiratory failure and confirmed a potential involvement of the ABO blood-group system. An association signal at locus 9q34.2 (rs657152) coincided with the ABO blood

**Table 3** Associated genetic polymorphisms

	Potential underlying working mechanisms	Reference
ABO blood group	The varied distribution of sialic acid-containing receptors on host cells' surfaces, modulated by ABO antigens, could influence the binding capacity of the virus's spike protein S1 to ACE2 and CD147 of the host cells.	[114]
	The presence of anti-A antibodies in patients with blood group type O and B may also modulate the interaction between the virus and host cells by the inhibition of the spike protein/ACE2-dependent adhesion to ACE2-expressing cells.	[115]
	Subjects with blood group type O have a downregulated IgM activity due to glycosylation and only bind the virus via hybrid H-type antigen formation. The IgM downregulation leads also to downstream anti-A and anti-B isoagglutinin activity, hallmarks of innate immune activity.	[116]
HLA system	Specific HLA genotypes can stimulate the T cell-mediated anti-viral response differently, possibly altering the symptomatology and transmission of the disease.	[117,118]
Haplogroup R	The involvement of androgens as well as Y linked genes together with the observation of statistical significant regional covariation between COVID-19 and haplogroup R1b, collectively point to a possible role of Y chromosome in COVID-19 severity.	
Neanderthal DNA	The risk allele GA of rs11385942 is associated with reduced expression of CXCR6 and increased expression of SLC6A20. OAS1 has a plausible biological activity against SARS-CoV-2 as they are part of the innate immune response against RNA viruses.	[119]

HLA, human leukocyte antigen; CXCR6, C-X-C chemokine receptor type 6; SLC6A20, Solute Carrier Family 6 Member 20; OAS1, 2'-5' oligoadenylate synthetase 1; RNA, ribonucleic acid.

group locus. A higher risk in blood group A was observed than in other blood groups, whereas blood group O showed a protective effect [119]. Other groups have identified subjects with blood type B as the most vulnerable group [128]. In comparison with the higher risk of severe illness or death

of blood group types A and AB, there is an agreement about the protective factor against SARS-CoV-2 infection of people with blood group O [125–127,129–131]. In contrast to the previous reports, some researchers did not find any association [132]. Besides, the C3 and ACE1 polymorphisms have been identified as more important confounders in the spread and outcome of COVID-19 in comparison with the ABO polymorphism. Similar to the majority of genetic polymorphisms, the ABO blood group polymorphism shows an east to a west gradient in Europe, which passively comigrates with causal human genetic factors involved in COVID-19. However, in comparison with the C3 polymorphism, which is a representative of the first principal component of European gene frequencies, the ABO\*A allele shows a weak association with the sixth principal component [133].

Several potential molecular mechanisms underlying the susceptibility of particular ABO blood types to COVID-19 have been proposed. A first hypothesis is the varied distribution of sialic acid-containing receptors on host cells' surfaces, which is modulated by ABO antigens through carbohydrate-carbohydrate interactions (CCIs). This phenomenon could influence the binding capacity of the virus's spike protein S1 via two domains [S1A (the N-terminal region, which interacts with sialic acid containing glycoproteins and glycolipids) and S1B (the receptor-binding domain)] to ACE2 and CD147 of the host cells [114]. Besides, ABH antigens, which are present on the erythrocyte membrane as well as many other cells (e.g., lymphocytes, platelets, and arterial and venular capillary endothelium) play a role in carbohydrate clustering, which facilitates CCIs, maximizing interaction, cell recognition, and aggregation. In comparison with antigen A, AB, and B, which stimulate carbohydrate clustering, the antigen characteristic of blood group type O (antigen H), does not induce carbohydrate promotion [134]. A second hypothesis is that the presence of anti-A antibodies in patients with blood group type O and B may also modulate the interaction between the virus and host cells by the inhibition of the spike protein/ACE2-dependent adhesion to ACE2-expressing cells [115]. A third hypothesis focuses on the host TMPRSS2, which is essential for spike protein priming and subsequent infection of SARS-CoV [135]. Proteolysis of viral serine by TMPRSS2 may allow for serine mobilization, a key molecule in mucin O-glycan. After hybridization to generate O-N-acetyl-D-galactosamine (O-GalNAc), the innate or specific immunity can be evaded by SARS-CoV-2 by hybridizing of ABO blood group, effectively mimicking self-cell presentation. An upregulated immunoglobulin M (IgM) activity is observed in patients with blood group type A, B, and AB, which facilitates a higher viral molecular contact

by A/B phenotypic-determining enzymes. Subjects with blood group type O have a downregulated IgM activity due to glycosylation and only bind the virus via hybrid H-type antigen formation. The IgM down-regulation leads also to downstream anti-A and anti-B isoagglutinin activity, hallmarks of innate immune activity [116]. Finally, the apparent protective effect of blood group O may be a consequence of lower ABO protein concentration, although the exact underlying mechanism has not yet been unraveled [136].

## 4.2 Human leukocyte antigen system

The human leukocyte antigen (HLA) system orchestrates immune regulation and plays an important role in many infectious diseases. The genetic variability of the MHC molecules can also affect the susceptibility and severity of SARS-CoV-2. Specific HLA genotypes can stimulate the T cell-mediated anti-viral response differently, possibly altering the symptomatology and transmission of the disease [117,118]. HLA-B\*07:03, HLA-B\*46:01, HLA-DRB1\*03:01, HLA-DRB1\*12:02 alleles have been reported to be associated with SARS-CoV-1 susceptibility, whereas HLA-DRB1\*03:01 was associated with a lower risk [137,138]. HLA class I molecules with a better theoretical capacity to bind SARS-CoV-2 peptides have been detected in mild disease and showed higher heterozygosity as compared with moderate and severe disease [139]. An *in silico* analysis of viral peptide-major histocompatibility complex (MHC) class I (HLA-A, HLA-B, and HLA-C) binding affinity revealed that HLA-A\*02:02, HLA-B\*15:03, and HLA-C\*12:03 effectively presented a larger amount of peptides, whereas the least efficient SARSCoV-2 peptide presentation was observed for HLA-A\*25:01, HLA-B\*46:01, HLA-C\*01:02 [140]. Another *in silico* analysis showed a possible association between HLA-A\*02:01 and an increased risk for and mortality due to COVID-19. In contrast, countries with a higher frequency of HLA-A\*24:02 or HLA-A\*11:01 had lower total confirmed cases per million population [141].

In East Asian populations, several HLA genotypes have been associated with increased susceptibility of COVID-19. In a small study of 82 Chinese COVID-19 patients, the SARS-CoV-1 susceptibility alleles (HLA-B\*07:03, HLA-B\*46:01, HLA-DRB1\*03:01, HLA-DRB1\*12:02) were present at a comparable frequency in COVID-19 patients. Besides, a significant association was found between HLA-B\*15:27 alleles and the occurrence of COVID-19 [142]. A significant positive association between

the HLA-B\*22 serotype and SARS-CoV-2 infection has been demonstrated in a cohort of 190 unrelated ethnic Chinese patients with confirmed COVID-19 from Hong Kong [143].

In a Russian case-control study of 111 COVID-19 patients and 428 healthy volunteers, there were no statistically significant differences in frequencies of HLA class I alleles in comparisons between deceased patients and control groups, and the deaths of adults vs. elderly subjects. Using a risk score based on the assignment of a numerical value to each allele associated with the aggregate binding affinity of viral peptides to the corresponding receptor, the presence of HLA-A\*01:01 allele was associated with high risk, while HLA-A\*02:01 and HLA-A\*03:01 mainly contributed to low risk of mortality due to COVID-19. Homozygosity by HLA-A\*01:01 accompanied early deaths, while only one HLA-A\*02:01 homozygote died before 60 years of age [144].

Through a population frequency analysis in the Italian population, it was demonstrated that HLA-A\*:01:01, HLA-B\*08:01, HLA-C\*07:01, HLA-DRB1\*03:01 and HLA-A\*02:01, HLA-B\*18:01, HLA-C\*07:01, HLA-DRB1\*11:04 had a regional distribution overlapping that of Covid-19 and showed a positive and negative significant correlation with COVID-19 incidence and mortality, respectively. A low incidence and mortality for COVID-19 were observed in the central-southern regions with high-frequency values of the haplotype HLA-A\*02:01, HLA-B\*18:01, HLA-C\*07:01, HLA-DRB1\*11:04 and of its alleles HLA-B\*18:01, HLA-C\*07:01 and HLA-DRB1\*11:04 in all their possible combinations containing at least one of such alleles [145]. A geographical ecological approach using data from the Italian Bone-Marrow Donors Registry suggested a permissive role of HLA-C\*01 and HLA-B\*44 towards SARS-CoV-2 infection [146]. In the Italian population, ~6% of the individuals carry HLA-DRB1\*08, 72% of whom are HLA-DRB1\*08:01, 8% HLA-DRB1\*08:02, 9% HLA-DRB1\*08:03, 9% HLA-DRB1\*08:04, 1% HLA-DRB1\*08:10, and all other subtypes with frequencies close to 0 [147]. None of these HLA-DRB1\*08 alleles was able to bind any of the viral peptides with high affinity, supporting the hypothesis that HLA-DRB1\*08-expressing individuals are less able to recognize SARS-CoV-2 and are more susceptible to infection and severe manifestations of COVID-19 [148]. In a small study of 99 Italian patients, HLA-B\*27:07, HLA-DRB1\*15:01 and HLA-DQB1\*06:02 showed a significant correlation with a severe or extremely severe course of COVID-19 [149]. Besides, HLA-DRB1\*08 represents a risk factor both for COVID-19

infection and related death [148]. In a Spanish observational and prospective study with 3886 healthy controls and a limited number of COVID-19 patients ( $n=72$  with 10 non-survivors), a higher rate of HLA-B\*39 and HLA-C\*16 were present in the patient group. The healthy subjects had a higher frequency of HLA-A\*32. After controlling for SOFA- or APACHE II score, the alleles HLA-A\*11 and HLA-C\*01 were associated with higher mortality, which was also the case for the allele HLA-DQB1\*04 after controlling for SOFA [150].

In Mexico, a significant negative correlation was found between the frequency of the class II HLA-DRB1\*01 allele and the fatality rate in hospitalized patients, based on bioinformatic predictions. This allele can present at least nine epitopes of the M protein and 11 of the N protein, revealing its high relevance for SARS-CoV-2 immunity [151].

Focusing on the global distribution of HLA gene polymorphisms, preliminary data from *in silico* analyses indicated a possible association between HLA-A\*02:01 and an increased risk for COVID-19 due to lower capacity to present SARS-CoV-2 antigens [141]. Investigating the association between HLA class I and the mortality of COVID-19 at a population level, HLA-C\*05 was identified as the most influential allele in increasing the risk of death [152]. Multiple *in silico* approaches to predict the population's response to the SARS-CoV-2 infection showed that HLA-A\*02:01, HLA-A\*01:01, HLA-A\*03:01, and HLAB\*07:02 were the most prevalent alleles in countries with the highest number of COVID-19 deaths per million, whereas HLA-A\*24:02, HLA-A\*11:01, HLA-B\*40:01, and HLA-A\*23:01 may contain protective effects [153].

### 4.3 Haplogroup R

Haplogroup R, or R-M207, is a Y-chromosome DNA haplogroup, which is numerous and widespread among modern populations. Some descendant subclades have been found since pre-history in Europe, Central Asia, and South Asia, whereas others have long been present, at lower levels, in parts of West Asia and Africa. In modern populations, haplogroup R1 (R-M173) appears to be comprised of subclades R1a and R1b (R-M420 and R-M343, respectively). The COVID-19 pandemic strikes strongly nations in which the R1b haplogroup has a high frequency, characteristic of Western Europe. More specifically, the R1b haplogroup spans from Northern Italy to Finisterre in northwestern Spain (69%), with a very high frequency in the Basque Country (90%), Ireland (81%), Great Britain (67%), Belgium

(61%) and France (58.5%) with two dominant regions: Brittany (80%) and Normandy (76%). The incidence of R1b in Italy shows a large variation by region. A higher incidence of COVID-19 has been observed in the region of Lombardy in comparison with the South of Italy. This corresponds with the high R1b frequency in the region between the Alps and Tuscan of more than 60% in the male population in comparison with the lower frequency in Calabria (25%) and Sicily (20%) [154]. In European countries, a strong correlation has been observed between the R1b-S116 haplotype frequency map and COVID-19 prevalence and mortality, respectively. Even in separate multivariate regression models for COVID-19 prevalence and mortality frequency, R1b-S116 remained a significant factor (next to ACE1 polymorphism for COVID-19 prevalence) [155]. In all countries or regions where R1b is dominant, COVID-19 incidence and death are remarkably higher than in countries where R1b is low or virtually non-existent. Almost all of the African continent and a good part of Asia, but also the European countries of the old Iron Curtain (R1) or the South, of which Greece (15%) is emblematic show a lower incidence of Sars-CoV-2 infections [154]. The involvement of androgens as well as Y linked genes together with the observation of statistical significant regional covariation between COVID-19 and haplogroup R1b, collectively point to a possible role of Y chromosome in COVID-19 severity.

#### 4.4 Neanderthal DNA

A segment of DNA 50,000 nucleotides long (corresponding to 0.002% of the human genome) on 3p21.31 containing 6 genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, and XCR1) [119], showed a strong association with severe COVID-19 infection and hospitalization (odds ratio: 1.6, 95% confidence interval: 1.42–1.79), but not with susceptibility. The risk allele GA of rs11385942 is associated with reduced expression of CXCR6 and increased expression of SLC6A20 [119]. Investigating whether the COVID-19 risk haplotype might have been introduced from our ancient relatives, Zeberg and Pääbo found the region to be closely related to that in the genome of a Neanderthal individual that lived in modern-day Croatia around 50,000 years ago, but it was not related to any known Denisovan genomes [156]. In the modern human population, this Neanderthal-derived haplotype occurs at a frequency of 30% in individuals who have a south Asian ancestry. However, 63% of the population in Bangladesh carries at least one copy of the Neanderthal variant, whereas 13%



of homozygotes are found. A frequency of 8% and 4% is found in Europeans and Latin Americans, whereas the risk haplotype is rare or completely absent in East Asians and Africans. The protective immune response mediated by these ancient genes might be overly aggressive, leading to the potentially fatal immune response observed in people who develop severe COVID-19 symptoms [156,157].

A large-scale, two-sample Mendelian randomization study of 931 proteins assessed for three COVID-19 outcomes in up to 14,134 cases and 1.2 million controls of European ancestry showed that increased 2'-5' oligoadenylate synthetase 1 (OAS1) concentrations in the non-infectious state are strongly associated with reduced risks of very severe COVID-19, hospitalization and susceptibility. A 50% decrease in the odds of very severe COVID-19 was observed per s.d. increase in OAS1 circulating levels [158]. OAS1 has a plausible biological activity against SARS-CoV-2 as they are part of the innate immune response against RNA viruses. In vitro studies have demonstrated that interferons and activate latent RNase L interferons induce OAS1 and activate latent RNase L, resulting in direct viral and endogenous RNA destruction [159]. As an interferon-stimulated gene [160], an association has been observed between OAS1 polymorphisms and the host immune response to several classes of viral infection [161–164]. A Neanderthal isoform of OAS1 in individuals of European ancestry affords this protection [158]. The protective alleles at rs4767027-T (the OAS1 pQTL) and rs10774671-G (the OAS1 sQTL) are found on a Neanderthal haplotype in populations outside of Sub-Saharan Africa [156], which was passed on to modern humans ~50,000–60,000 years ago [165]. In comparison with the rs4767027-T allele, which is derived from the Neanderthal lineage, Neanderthals preserved the ancestral state of the rs10774671-G allele. The rs10774671-G allele regulates OAS1 alternative splicing, which increases the isoform p46. This is the only OAS1 isoform, which is robustly upregulated during infection [166] and has a higher enzymatic activity against viruses than the p42 isoform [167]. The Neanderthal haplotype has undergone positive selection in Europeans with an rs4767027-T allele frequency of 0.32 [165]. Higher OAS3 concentrations have been associated with worse COVID-19 outcomes, which is an opposite direction of effect compared to OAS1, which might reflect complex biology of OAS genes for innate immune response. Based on functional studies demonstrating the antiviral effect of OAS genes, OAS1 might be the main driver of the protective effect of the p46 isoform for COVID-19 outcomes [166].



## 5. Conclusion

The present review provides some hypotheses about the role of host polymorphisms in the pathogenesis and outcome of COVID-19, rather than definitive information about the nature of associations between polymorphisms and COVID-19. The above-mentioned correlations do not mean a causal relationship between these polymorphisms and the prevalence and outcome of COVID-19. Despite the correlation between this risk haplotype and clinical outcomes, genetics alone do not determine a person's risk of developing severe COVID-19. Our genes and their origins influence the development and progression of COVID-19, but environmental factors also have key roles in disease outcomes [157].

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