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## Hypotheses and facts for genetic factors related to severe COVID-19

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### Abstract

Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe coronavirus disease 2019 (COVID-19). Hence, it seems that genetics matters here, as well. Nevertheless, the virus's nature, including its RNA structure, determines the rate of mutations leading to new viral strains with all epidemiological and clinical consequences. Given these observations, we herein comment on the current hypotheses about the possible role of the genes in association with COVID-19 severity. We discuss some of the major candidate genes that have been identified as potential genetic factors associated with the COVID-19 severity and infection susceptibility: *HLA*, *ABO*, *ACE2*, *TLR7*, *ApoE*, *TYK2*, *OAS*, *DPP9*, *IFNAR2*, *CCR2*, etc. Further study of genes and genetic variants will be of great benefit for the prevention and assessment of the individual risk and disease severity in different populations. These scientific data will serve as a basis for the development of clinically applicable diagnostic and prognostic tests for patients at high risk of COVID-19.

**Key Words:** Genome-wide association studies; Severe COVID-19; SARS-CoV-2; *ACE2*; *TLR7*; *ApoE*; *TYK2*; *OAS*; *DPP9*; *IFNAR2*; *CCR2*

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**Core Tip:** Understanding what contributes to the development of severe coronavirus disease 2019 (COVID-19) can be of considerable clinical and therapeutic advantage. Severe acute respiratory syndrome coronavirus 2 infection may present with different COVID-19 manifestations, where various host genetic factors influence the viral susceptibility, immune response, disease progression, and outcomes. Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe COVID-19. Hence, it seems that genetics matters here, as well.

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## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19) that emerged in Wuhan, China, in December 2019 and its rapid spread all over the world. COVID-19 was declared a pandemic by the World Health Organization in March 2020. Since then, it has become the leading burden for healthcare[1]. Although healthcare workers have been facing the disease for almost a year, the management of COVID-19 is still a challenge because of the clinical course it may take. On the one hand, about 40% of SARS-CoV-2 infected people present with mild or no symptoms. At the same time, moderate illness is observed in another 40% of them. On the other hand, about 15% manifest with symptoms of pneumonia that requires hospital admission and oxygen support, and 5% develop a critical illness, complicated with respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury[2]. Regarding the World Health Organization data, since the pandemic was declared, more than 2.4 million deaths have been reported to date[3]. Some of the risk factors considered predisposing to a severe course of COVID-19 and higher mortality rates include: Advanced age and smoking, underlying chronic conditions affecting the cardiovascular system, the lungs, and the kidneys, as well as immunosuppression and cancer [4]. However, there is still a lack of predictive features and signatures for severe COVID-19.

Additionally, the clinical course of COVID-19 is closely related to the severity of the inflammatory response conducted by the immune system activation. A complex interaction involving immune cells, cytokines, and mediators leads to systemic immune reactions, which might result in immune hyperactivation or dysregulation. Hence, the cytokine storm is caused by the uncontrolled inflammatory response, and it is crucial for illness's severity and the development of ARDS, multiorgan failure, and fatal outcome[5,6]. Clinical laboratory results might serve useful functions as biomarkers in the management of COVID-19 and prediction of the probable outcome [7]. Laboratory findings in the severe course of COVID-19 usually include low lymphocytic count and hypoalbuminemia, significant elevation of liver transferase enzymes, C-reactive protein, lactate dehydrogenase, ferritin, and D-dimer, along with high levels of some cytokines[8]. However, the influence of various host genetic factors on viral susceptibility, immune response, disease progression, and outcomes has been discussed recently[9,10]. Genome-wide association analysis allows the identification of potential candidate genes involved in the development of severe COVID-19. Hence, it seems that genetics matters here, as well. Nevertheless, the virus's nature, including its RNA-genome, determines the enhanced rate of mutations leading to a new viral genome with significant epidemiological and clinical consequences. Given these observations, we herein comment on the current hypotheses about the possible role of the genes for COVID-19 severity. We discuss some of the major human candidate genes that have been identified as potential genetic factors associated with the

different COVID-19 severity and infection susceptibility.

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## MAIN CONVENTIONAL RISK FACTORS FOR SEVERE COVID-19

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The factors that predispose to a severe course of COVID-19 are of great importance for infection confinement among people from risk groups. Age, gender, and comorbidities, particularly cardiovascular diseases, should be taken as risk factors that depend on one another[11].

In numerous recent research studies, based on the clinical course of COVID-19, age is discussed as a leading risk factor. On the one hand, most of the viral infections affect children, whereas SARS-CoV-2 infection typically occurs in people of advanced age, which might be due to the increased comorbidities as well as to the age-dependent gene expression. In a published study, the death rate among people older than 80 was 14.8%. In contrast, the percentage among those between 70-79.9 years was 8% and 3.6% among those between 60-69.6 years. Owing to the latter, provided the same comorbidities, the younger the age, the lower the death rate is[12].

Gender and its significance as a risk factor are difficult to be evaluated due to the differences in the socio-economical status, lifestyle, and quality of life between men and women. Furthermore, cardiovascular and chronic pulmonary diseases are more frequently observed in men. Moreover, tobacco and alcohol abuse are usual for the male gender and might as well cause respiratory, liver, gastrointestinal illnesses, *etc.* Alternatively, women are commonly involved in caring for sick family members at home and patients at hospital centers, as most nurses are women[13]. Therefore, females are exposed to an increased risk of COVID-19 contraction. Additional factors such as socioeconomic status, menopausal transition, pregnancy and complications during pregnancy, fertility treatment, hormone contraceptive usage, postmenopausal hormone replacement therapy, breast cancer as well as prostate cancer anamnesis are recognized to have an impact on the differences in the COVID-19 course in men and women. Recently, more pieces of evidence have been accumulated about different gender-dependent expression of proinflammatory cytokines such as tumor necrosis factor-alpha and interleukin (IL)-12, which play a significant role in the systemic inflammation and cytokine storm[14-16]. According to published data, the death rate is assessed to be 2.5% in the male gender, while in females it is 1.7%. Nevertheless, these values do not provide proof of more severe COVID-19 for men[13].

Additionally, investigations of the laboratory changes in patients with COVID-19 have shown considerably elevated levels of lactate dehydrogenase, alanine transaminase, gamma-glutamyl transaminase, C-reactive protein, IL-6, erythrocyte sedimentation rate, ferritin, coagulation factors (including D-dimer and fibrinogen), along with significant anemia and lymphopenia in patients with accompanying disease in comparison to those without. These findings suggest that underlying comorbidities increase the risk for an uncontrollable inflammatory reaction, hypercoagulation, and excessive release of tissue-damaging enzyme, hence more severe COVID-19[17].

Another critical observation has shown the majority of those diagnosed with COVID-19 had type 2 diabetes. This metabolic illness affects the whole organism and the immune system and, by misbalancing its function, predisposes to infections. Moreover, SARS-CoV-2 disturbs glucose metabolism and increases the insulin requirements of the organism. Thus, diabetes and obesity should be considered risk factors for a severe course of the coronaviral infection as well[17].

Interestingly, during the first wave of COVID-19 in the United Kingdom, younger and less burdened by comorbid illnesses patients were also admitted to intensive care units[18]. These data have only shown us that there might be other factors, including genetic background, related to the severity of COVID-19.

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## CHARACTERISTICS OF CRITICALLY ILL COVID-19 PATIENTS

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COVID-19 manifests with various or no symptoms. Despite having no symptoms, an asymptomatic person can also be a source of the infection. In symptomatic COVID-19 cases, the symptom onset is after an average incubation period of 5-6 d (up to 14 d). However, there are no specific and pathognomonic symptoms of the illness[5,8]. COVID-19 patients usually present with fever, dry cough, appetite loss, as well as sore throat, nasal congestion, malaise, headache, diarrhea, nausea, and vomiting. Some of the patients experience anosmia and ageusia. People of advanced age may present

with qualitative and quantitative consciousness disorders and lost mobility. Dyspnea and shortness of breath are typically observed in severe cases[19].

Disease physiology includes damage of type 2 pneumocytes, viral pneumonia, cytokine storm, macrophage-activation syndrome, ARDS, disseminated intravascular coagulation, sepsis, and general immune dysregulation, all of which can be combined or present simultaneously[20].

Most of the SARS-CoV-2 infected experience mild to moderate symptoms. Fifteen percent of the patients present with pneumonia that requires hospital admission. According to published data, patients in hospitals develop dyspnea about 5 d after symptom onset. On the contrary, in severely ill patients, the disease may rapidly progress to multiorgan failure[21-23].

A typical complication of SARS-CoV-2 infection is the development of ARDS. The latter is presumed the leading cause of death in patients with COVID-19, particularly among those with underlying diseases and conditions, assessed as risk factors, smokers, and older ones. The immunological events during COVID-19 cause not only severe harm and ventilation collapse of the lung parenchyma, but perhaps, it would eventually lead to complications later in life[5]. Additionally, inflammation destroys the endothelium and contributes to the release of the plasminogen tissue activator that can contribute to COVID-19 associated thromboembolic complications consistent with a hypercoagulable disease. Although the primary cause of death in COVID-19 is thought to be ARDS, the problem associated with bradykinin B1 receptor activation in the lung endothelial cells is another serious cause for severe COVID-19, as well as sepsis-associated disseminated intravascular coagulation[24]. Thromboembolic events are among the most commonly observed complications in COVID-19. Its incidence is higher in critical illness, despite the anticoagulant administration. Thromboembolism may manifest as deep vein thrombosis, pulmonary thromboembolism or may lead to myocardial infarction or cerebral ischemia[21]. We hypothesize that complement overactivation and C1-esterase hyperproduction could be another cause of thromboembolic complication in severe COVID-19.

COVID-19 manifests as a severe illness in patients with underlying chronic conditions, including cardiovascular diseases, hypertension, diabetes, and renal disease. Moreover, the mortality rate is higher among these patients, whereas infants and children experience milder disease, and the mortality rate among them is comparatively lower[21,25,26]. Furthermore, between 3%-29% of the patients develop complications that require intensive care, and the approximate mortality rate is 38% [21,23]. Within a week after the symptoms worsen, pneumonia progresses to ARDS. Along with ARDS, critically ill patients may also develop extrapulmonary manifestations, some of which are cardiovascular, neurological, and gastrointestinal disorders, renal impairment, thromboembolism, sepsis, and septic shock[1,21].

Amongst them, the disorders of the cardiovascular system include myocardial ischemia, myocarditis, myocardial injury, arrhythmias, and cardiogenic shock. Neurological manifestations are observed in about 36% of the patients with severe COVID-19, presented as dizziness, headache, ageusia and anosmia, myalgia, or with more severe manifestations such as acute stroke, consciousness disorders, Guillain-Barré syndrome, meningoencephalitis, and necrotizing encephalopathy, which affects the brain stem and basal ganglia. Acute liver and kidney injuries (31%) are also observed, whereas gastrointestinal bleeding rarely occurs. Elevation of the liver enzymes and the bilirubin level might correlate with the severity of the disease[21].

Critically ill COVID-19 patients may develop sepsis as a result of host response dysregulation to infection, leading to organ dysfunction. It clinically presents with respiratory failure, impaired tissue oxygen supply, tachycardia, hypotension, oliguria, coagulopathy, *etc.* Septic shock occurs in extreme hypotension that is ineffectively treated with infusions and requires vasopressor application[27]. Collectively these observations have shown that a certain genetic background is required.

Besides, the recently published Genome wide association study suggests that individuals with blood group A be predisposed to a severe COVID-19, whereas those with blood group 0 might be at lower risk for developing critical illness[28].

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## GENETIC ASSOCIATION STUDIES AND COVID-19 HOST GENETICS INITIATIVE

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In recent years, genome-wide association studies (GWAS) have offered the possibility of detecting the most common genetic variants associated with various diseases. To date, a large number of single nucleotide substitutions have been found in different

genes or regulatory regions (polymorphic variants) in the genome that can explain the severity and pathology of these diseases.

In a GWAS that involved patients with severe COVID-19 at seven hospitals in Italy and Spain and a meta-analysis of the two case-control panels, 8582968 single-nucleotide polymorphisms (SNPs) were analyzed. It was identified that the first gene cluster of chromosome 3 covers six genes (*3p21.31-SLC6A20, LZFTL1, CCR9, CXCR6, XCR1, and FYCO1*) that aggravate the COVID-19 disease[28]. This study showed the potential involvement of the ABO blood-group system. Other GWAS papers reported results about risk loci in chromosome 19p13.3, 12q24.13, and 21q22.1 associated with severe COVID-19[29]. Some genes belong to the type I interferon pathway and predispose to life-threatening COVID-19 pneumonia. Five common variants were identified (rs3787946, rs9983330, rs12329760, rs2298661 and rs9985159) at locus 21q22.3 within transmembrane serine protease (TMPRSS)2 that showed associations with severe COVID-19[30].

### **Chromosome 3p21.31**

At locus 3p21.31, the association with severe COVID-19 signal spanned the genes *SLC6A20, LZFTL1, CCR9, FYCO1, CXCR6, and XCR1*. A candidate in this region is *SLC6A20*, which encodes the *SIT1* (sodium–amino acid transporter 1). It functionally interacts with angiotensin-converting enzyme 2 (*ACE2*), which SARS-CoV-2 uses for entering the cells[31,32]. The locus also contains genes encoding *CCR9* and *CXCR6* (chemokine receptors of the C-C and CXC families). They control the cell migration associated with the immune system by trafficking effector cells to the sites of inflammation, especially in the immune response to airway pathogens, including influenza viruses[28,33,34].

A meta-analysis has found a significant association between the severe COVID-19 disease and rs11385942 at locus 3p21.31 and rs657152 at locus 9q34.2. Leucine zipper transcription factor-like 1 (*LZFTL1*) might be the most important, with the rs11385942 variant. *LZFTL1* is expressed mainly in human lung cells. It encodes a protein involved in the immunologic synapse with antigen-presenting cells such as dendritic cells[35,36]. Reduced expression of *CXCR6* and enhanced expression of *SLC6A20* were related to the risk genotype GA of rs11385942. The frequency of the risk allele at 3p21.31 (rs11385942) was increased among patients on mechanical ventilation than those who received only oxygen supplementation. Available database variants suggest that the frequency of this risk allele varies among populations worldwide[28].

### **ABO locus**

A genome wide association analysis has identified the locus 9q34.2 where the rs657152 is located and also includes the ABO blood group locus. A blood-group analysis demonstrated a higher risk for people with blood group A and a protective effect in people with blood group O as compared with other blood groups[28,37]. Variation in the *ABO* gene is the basis of the ABO blood group. Since the 'O' blood group is caused by a deletion of guanine-258 near the N-terminus of the protein, this results in a frameshift mutation and translation of an almost entirely different protein. This 9q34.2 locus has also been identified as a susceptibility locus for severe COVID-19. Using the combinations of genotypes of three different SNPs, a higher risk among individuals with blood group A and a protective effect of blood group O in the Spanish and Italian analyses was reported[28]. A similar study in China in March 2020 showed that blood group A was associated with a significantly higher risk of COVID-19 compared with the other blood groups[37,38].

### **Human leukocyte antigen (HLA) analysis**

HLA region (6p21.33) was analyzed with GWAS. The spike protein and the nucleocapsid proteins of the SARS-CoV-2 are reported to contain multiple class I epitopes with predicted HLA restrictions. Individual HLA genetic variations can explain different immune responses to different viruses across the population. Nguyen *et al* [39] reported the potential associations between the genetic variants in major histocompatibility complex class I genes (*HLA A, B, and C*) and the severity of COVID-19. The fewest binding peptides for SARS-CoV-2 were found for *HLA-B\*46:01*, suggesting that individuals with this allele should be more vulnerable to COVID-19 [40]. Conversely, the highly conserved SARS-CoV-2 peptides that are shared among common human coronaviruses were detected for *HLA-B\*15:03*, suggesting that individuals could be protected with T cell immunity[29,39]. Another published report from Italy defined other three HLA alleles-*HLA-DRB1\*15:01, -DQB1\*06:02, and -B\*27:07*, which may predispose to a less favorable outcome and severe COVID-19[41].

Preliminary results from China also indicated that the HLA-A\*11:01, -B\*51:01, and -C\*14:02 alleles predispose patients to the worst clinical outcome[42]. Much more studies are needed to understand fully the role of single HLA alleles in COVID-19 severity.

Recently, the HLA system has been under thorough investigation for its crucial role in autoimmunity and infectious disease susceptibility[10,40]. A strong association has been established between the HLA region and autoimmune diseases such as type 1 diabetes (T1D - DR3; DR4; DQB1), multiple sclerosis (MS-DR3), rheumatoid arthritis (RA-DRB1; DR4), Graves' disease (GD-DR3; DRB1\*08; B\*08; C\*07), ankylosing spondylitis (AS-B27), systemic lupus erythematosus (SLE-DR3; DR8; DR15), Hashimoto's thyroiditis (HT-DR3; DR4), narcolepsy (DQ6), Addison's disease (DR3), and multiple sclerosis (MS-DR15)[43-45]. Nevertheless, a comprehensive explanation of the link between autoimmune diseases and infection susceptibility is yet to be given.

### **TMEM189-UBE2V1**

GWAS in China analyzed 22.2 million genetic variants in 332 COVID-19 patients from the Shenzhen Third People's Hospital. During hospitalization, 64 laboratory analyses were performed for each of the patients to classify their severity condition based on the demographic features age and gender as well as medical comorbidities and treatments[42]. The features of greatest importance that contribute to more severe disease outcomes included decreased lymphocyte and platelet counts, increased C-reactive protein, D-dimer, IL-6, age, and concomitant diseases[29,46]. Obviously, the genes that encode proteins of the immune system are responsible for the disease severity.

The most significant SNP, rs6020298, is located in the intron of the transcript TMEM189-UBE2V1 in the 20q13.13 region. This SNP also affects the genes *UBE2V1* and *TMEM189*. TMEM189-UBE2V1 has been involved in the IL-1 signaling pathway [47]. In COVID-19 patients, IL-1 is elevated, especially in the critically-ill ones who suffer from the cytokine storm[48]. TMEM189-UBE2V1 has a lot of functional associations with the biological processes in different cell types and tissue, but the main function of its protein product has not yet been determined.

### **ACE2 and TMPRSS2**

Depending on virus strains and cell types, coronavirus spike proteins may be cleaved by one or several host proteases-neutrophil elastase (ELANE), furin, cathepsins, TMPRSS-2, and TMPRSS11A[49-53].

The availability of these proteases on the target cells determines whether the virus particles enter the cells through the plasma membrane or endocytosis. SARS-CoV-2 infection of the host depends on two factors: The ACE2 receptor for the viral entry and the TMPRSS2 for the viral spike protein priming[54]. A recently published comparative genetic analysis in different populations has shown possible associations between the coding region variants of ACE2 and TMPRSS2 with COVID-19 severity and outcomes[30].

The *ACE2* gene, located on chromosome Xp22.2, exhibits a high level of polymorphism. The ACE2 receptor is highly expressed in the alveolar type-2 cells in the lung but also in the proximal kidney tubules, liver cholangiocytes, esophagus keratinocytes, myocardial cells, bladder cells, and gastrointestinal epithelial cells[55, 56].

SARS-CoV-2 enters the cell by binding to the ACE2-an integral membrane protein that catalyzes the production of angiotensin 1-7 from angiotensin II[57]. ACE2 is expressed on the vascular epithelium, renal tubular epithelium, and Leydig cells in the testes. In the respiratory system, ACE2 is mainly expressed on type II pneumocytes [54]. After the viral spike protein binds to the ACE2, the S-protein undergoes structural changes through proteolysis by the receptor TMPRSS2[58]. These changes are essential for the fusion between the cellular and viral membrane and the following viral RNA release. In the host cell, the viral genome uses the cellular machinery for new virions formation[6,59]. In the respiratory system, the pneumocytes type II are the target cells that SARS-CoV-2 attacks. Persistent target cell infection leads to ACE2 downregulation and subsequent ACE2 deficiency[59]. The latter prevents angiotensin II conversion to angiotensin I. Angiotensin II excess activates the angiotensin II type 1 receptor and results in vasoconstriction and various physiological effects that include inflammation, fibrosis, thrombosis, and reactive oxygen species (ROS) production. On the other hand, angiotensin has opposite functions by binding to specific receptors, it causes vasodilation, anti-inflammation, anti-fibrosis, anti-thrombosis, and ROS neutralization. That is why ACE2 is considered to provide protection from ROS production in the inflammatory process. Moreover, ACE2 controls the macrophages'

overexpression of tumor necrosis factor- $\alpha$  and IL-6, both playing an essential role in the inflammation[60,61]. Thus, the ACE2 deficiency leads to an imbalance of the renin-angiotensin system, which appears to be a crucial mechanism in COVID-19 pathogenesis[62].

Owing to the fact that the *ACE2* gene is located on the X chromosome, it has been suggested that the higher mortality rate among males should possibly be related to its lower expression. Furthermore, estrogen increases the ACE2 expression and activity in women[63,64]. Renin-angiotensin system balance is maintained by the ACE and ACE2 function; thus, *ACE2* gene variants or their overexpression lead to renin-angiotensin system imbalance resulting in vasoconstriction, hypercoagulation, fibrosis, alveolar cell apoptosis, increased ROS production, and lung damage overall. Common gene polymorphism might alter both *ACE* and *ACE2* gene expression and have a similar effect. It is possible for ACE/ACE2 balance to be influenced by other gene products, for instance, ABO locus, angiotensinogen (AGT), sex-determining region Y gene, SOX3, A disintegrin and metalloprotease 17, angiotensin II receptor type 1, and angiotensin II receptor type 2[10,62,65,66]. Allele frequency variations of the *ACE2* gene in different populations might be due to SNPs. Compared to a global average, the protective variants were found to be of higher frequency in the Asian population, whereas the risk variants were more frequent among the population of European descent[10,63].

Polymorphisms in *ACE2* were found to associate with pulmonary and cardiovascular conditions by altering the AGT-ACE2 interactions, such as p.Arg514-Gly in the African and African-American populations[30].

*TMPRSS2* is localized in 21q22.3 and is a key gene in prostate cancer. The product of the gene is plasma membrane-anchored serine protease that participates in proteolytic cascades for the normal physiologic function of the prostate[67,68].

Matsuyama *et al*[69] demonstrated that *TMPRSS2*-expressing cell lines are highly susceptible to SARS-CoV, Middle East respiratory syndrome coronavirus, and SARS-CoV-2. The susceptibility to COVID-19 could be explained with prevalent polymorphism Val160Met (rs12329760) in *TMPRSS2*. The harmful effect of the rs12329760 polymorphism in the coding region of the *TMPRSS2* gene has been confirmed by a recent study that used data of the 1000 genome project[70]. The p.Val197Met missense variant that impacts the *TMPRSS2* protein stability demonstrated a decreasing allele frequency among the severe patients compared to the higher frequency in the asymptomatic and mild groups. This variant is associated with valine to methionine alteration at the 197<sup>th</sup> amino acid (p.Val197Met). This results in a decrease in the *TMPRSS2* protein stability and ACE2 binding[70]. Moreover, p.Val197Met was previously found to exhibit greater allele frequency in East Asians (0.31–0.41) and Finnish (0.36) but not in South Asians (0.14–0.29) and Europeans (0.17–0.23)[71]. The study of Chinese patients has shown a reduced allele frequency of the p.Val197Met missense variant. That variant affects the stability of the *TMPRSS2* protein in the severely infected compared to the mildly infected patients and the general population [42]. The localization of the *TMPRSS2* gene on 21q22.3 suggests that people with Down syndrome are more prone to COVID-19 infection[30].

A recently published study from Italy has identified a number of *ACE2* variants with a potential effect on the spike protein stability[72]. Three missense changes may interfere with the protein structure and stabilization, p.(Asn720Asp), p.(Lys26Arg), and p.(Gly211Arg). Two rare variants, p.(Leu351Val) and p.(Pro389His), affect the binding and entry of the spike of SARS-CoV-2[40]. Exome sequencing of COVID-19 patients from Italy for genetic variants of *TMPRSS2*, *PCSK3*, *DPP4*, and *BSG* genes identified 17 variants[73].

### **The X-chromosomal toll-like receptor (TLR7)**

TLRs are highly conserved from *Drosophila* to humans. They mediate the production of cytokines that are necessary for the development of effective immunity. The various TLRs exhibit different patterns of expression, TLR7/8 can identify the single-stranded RNA ssRNA of the virus. The immunoinformatic approach revealed that the SARS-CoV-2 genome has more single-stranded RNA fragments that could be recognized by TLR7/8. These findings suggest the innate immune hyperactivation by SARS-CoV-2 and the possibility to provoke a strong proinflammatory response *via* TLR7/8 recognition and to cause severe lung injury, as well[74].

By whole-exome sequencing of the patients and family members in the Netherlands, there have been identified loss-of-function variants of the *TLR7* gene in X-chromosome (Xp22.2) associated with impaired interferon type I and II responses. The first family possessed a 4-nucleotide deletion [c.2129\_2132del; p.(Gln710Argfs\*18)], which was maternally inherited; and in the affected members of the second family, a

missense variant [c.2383G>T; p.(Val795Phe)] in TLR7 was observed. Thus, TLR7 seems to be an essential component of the innate immune response against SARS-CoV-2[29, 75-77]. The study has also provided an explanation for the higher fatalities from COVID-19 in men than in women. Several immune-related genes have been found in the X chromosome. The males are hemizygotes on the X chromosome that they inherit from their mothers. Therefore, any abnormality in the X chromosome genes is more likely to be expressed phenotypically and have more pronounced immunological consequences. Females carry both a maternal and a paternal X chromosome, and due to X chromosome inactivation, they are functional mosaics for X-linked genes[77-79]. Loss-of-function mutation in the *TLR7* gene gives evidence that genetic errors in interferon (IFN)-I and II pathways contribute to severe COVID-19.

### **Apolipoprotein E (ApoE)**

ApoE is synthesized in brain astrocytes, adipocytes, hepatocytes, and arterial wall macrophages. For their role in lipid transport, ApoE is critical for brain, immune, and vascular functions[80-83].

Dementia, cardiovascular disease, and type 2 diabetes were identified as major risk factors for severe COVID-19 in older individuals in the United Kingdom[84-86].

The *APOE* gene, with its three major isoforms APOE2, APOE3, and APOE4, is encoded by  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$  alleles. The ApoE  $\epsilon 4$  genotype is associated with dementia and delirium[85], and the  $\epsilon 4\epsilon 4$  homozygous genotype are at a 14-fold increased risk of Alzheimer's disease[86].

Using the United Kingdom Biobank data, associations between ApoE  $\epsilon 4$  alleles and COVID-19 severity have been found. ApoE homozygotes have a 2.2-fold higher risk for severe COVID-19, independently of major risk factors, and 4.3-fold higher case-fatality after COVID-19 than ApoE  $\epsilon 3$  homozygotes[84,85]. The heterozygotes ( $\epsilon 3/\epsilon 4$ ) are at lower risk.

If the ApoE  $\epsilon 4$  allele has an influence on COVID-19 severity, this may explain the prevalence of severe disease amongst certain ethnicities. According to a study, the allele frequency was 29.5% for homozygous individuals vs 12.1% for the Caucasian group[87]. Furthermore, till April 2020, 34% of the COVID-19 deaths in the United States occurred amongst homozygotes, despite the population representing only 13% of all Americans[88]. ApoE  $\epsilon 4$  may have multiple effects in COVID-19, which may also be reflected in ethnicity.

### **Interferon-induced transmembrane protein 3 (IFITM3)**

Five IFITM genes (interferon-induced transmembrane proteins) have been identified in humans, *IFITM1*, *IFITM2*, and *IFITM3*, as well as *IFITM5* and *IFITM10* with unknown immunity role[89]. Interferon-induced transmembrane proteins are a family of small proteins that are localized in the plasma and endolysosomal membranes. They inhibit viral entry into the host cells and reduce the production of infectious virions. Many SNPs have been identified in these genes, some of which have been associated with the severity of the viral infection.

*IFITM3* gene variants have been related to distinctive clinical responses to viruses like influenza A (H1N1) virus, Marburg virus, Ebola virus, West Nile virus, human immunodeficiency virus type 1, vesicular stomatitis virus, and dengue virus[42-48]. A human *IFITM3* SNP rs12252 C/T was associated with the severity of avian influenza and severe illness with influenza H1N1/09. The *IFITM3* rs12252 has also been associated with the progression of human immunodeficiency virus type 1 infection [90]. Two polymorphisms have been found to have an association with a severe COVID-19, rs12252-C and rs34481144-A. The SNP rs12252-C/C in the gene *IFITM3* was detected for the first time in a mild-to-moderate COVID-19 patient from Wuhan, China that required hospitalization but eventually recovered[91]. However, this SNP's prevalence was found to be 26.5% in the Chinese population[92]. The results have shown an association between *IFITM3* rs12252 polymorphism and the risk of COVID-19 and patient hospitalization[93,94].

Recently, the *IFITM3* gene rs12252 has been associated with the severity of COVID-19 in a cohort of 80 patients admitted to Beijing Youan Hospital[55,56]. Patients were classified as mild and severe, and CC-homozygotes were among the severe cases. The rs12252 C frequency was significantly higher among Chinese compared to individuals of European ancestry. Another study was conducted to determine the link between *IFITM3* rs12252 and the risk of developing severe COVID-19 in a Spanish cohort[93].

The significance of the *IFITM3* rs12252-C polymorphism for severe COVID-19 seems to be population-dependent. The second *IFITM3* SNP, rs34481144-A, was not reported to influence the severity of COVID-19 in humans.

### **Cathepsin B/Cathepsin L**

SARS-CoV-2 uses ACE2 as an entry receptor[95], and TMPRSS2 for the spike protein priming[54]. SARS-CoV-2 could also use cathepsin B (CTSB) or cathepsin L (CTSL) entering TMPRSS2-negative cells[96].

Three variants in the active sites for CTSB (two missense variants and one synonymous variant) and one missense variant for CTSL were found. Although all missense variants on active sites of CTSB/L are associated with severe disease, their allele frequency (AF) was very low (AF < 0.01%). CTSB has 429 nonsynonymous variants including 51 loss-of-function variants (all with AF < 0.01%). CTSL has 211 nonsynonymous variants including 17 loss-of-function variants[97].

Cardiac damage related to SARS-CoV-2 has been attracting more and more attention. The mechanism of cardiovascular injury caused by COVID-19 has not been fully elucidated yet[98].

The increase in the ACE2 and CTSL expression levels creates a favorable condition for the SARS-CoV-2 to invade the heart, and these patients may experience severe cardiac injury. In addition, cytokine storm in severe COVID-19 can aggravate the myocardial damage[99,100].

### **Piezo-type mechanosensitive ion channel component 1 (PIEZO1)**

There is evidence that membrane proteins such as ACE2 and TMPRSS2 are important in SARS-CoV-2 entry[54,101]. It is indisputable that viral entry is affected by other membrane proteins and lipids[102,103].

Membrane proteins are ion channels[104,105] embedded in the membrane. They allow transmembrane flux of ions such as Ca<sup>2+</sup>, an ion that fulfills regulatory functions in coronaviral mechanisms[106,107].

*PIEZO1* gene encodes a non-selective cation channel that mediates endothelial responses to blood flow. It forms Ca<sup>2+</sup>-permeable non-selective cation channels with the capability to respond to membrane tension caused by fluid flow along the endothelial membrane surface[108]. *PIEZO1* indents the membrane in an inverted dome-like fashion and therefore modifies the overall structure of the membrane[109]. There is increasing evidence of its roles in many aspects of endothelial function, such as angiogenesis[100] and pulmonary vascular permeability. It also regulates IL-6, which is a key inflammatory mediator of COVID-19[110].

The genome associate analysis suggests three missense *PIEZO1* SNPs (rs7184427, rs6500495, and rs7404939) associated with COVID-19 fatality independently of the risk factors. All of them affect amino acids in the proximal N-terminus of *PIEZO1*. Human *PIEZO1* comprises 2521 amino acids in total, and rs6500495 affects position 83, rs7404939 position 152, and rs7184427 position 250. rs6500495 encodes a switch at position 83 from the reference isoleucine to threonine; rs7404939 encodes the reference proline rather than leucine at position 152, and rs7184427 encodes alanine rather than the reference valine at position 250.

A genome sequence analysis showed that these SNPs vary in prevalence with ethnicity and that the most significant SNP (rs7184427) varies between 65% to 90%. The analysis also suggests that rs7184427 affects a residue that is highly evolutionarily conserved and therefore has functional importance for COVID-19 severity and fatality [101].

### **Interferon- $\alpha/\beta$ receptor (IFNAR), tyrosine kinase 2 (TYK2), Oligoadenylate synthetase 1 (OAS1), dipeptidyl peptidase 9 (DPP9), and CC chemokine receptor 2 (CCR2)**

Recently, the Genetics of Mortality in Critical Care (GenOMICC, <https://genomicc.org/>) GWAS, which involved 2244 COVID-19 critically ill patients in the United Kingdom intensive care units, has reported robust genetic predisposition related to essential antiviral host defense and inflammatory mediators, associated with severe COVID-19 inflammatory organ damage[24]. It has shown that the low expression of IFNAR2 or the high expression of TYK2 was related to life-threatening illness. In addition, the high expression of the monocyte-macrophage chemotactic receptor CCR2 correlates with extreme COVID-19 viral spread in the lung tissue.

The GenOMICC study has also revealed that hospitalized COVID-19 patients were affected by alterations in two biological mechanisms: Innate antiviral defenses and host-driven inflammatory lung injury. In the early disease, IFNAR2 and interferon-inducible OAS gene cluster (*OAS1*, *OAS2*, *OAS3*) have been considered critical, whereas in the late and life-treating disease, the most important are DPP9, TYK2, and CCR2[24,111].

It is well-established that interferons are essential during viral infection; thus, the increased IFNAR2 interferon expression decreases the chances of serious COVID-19

[111]. Since the *IFNAR2* gene has a protective role for severe COVID-19, it was shown that rare loss-of-function mutations in *IFNAR2* were related to severe disease and many other viral diseases[112]. One can speculate that interferon administration may reduce the probability of critical COVID-19. However, this was not confirmed by the studies[113]. Furthermore, IFN deficiency, in particular IFN-I, was documented during SARS-CoV-2 infection. These deficiencies can occur by inherited mutations in the genes encoding key antiviral molecules or by producing antibodies that bind and 'neutralize' IFN-I[114]. The latter is mostly seen in severe COVID-19 patients[115]. Zhang *et al*[116] reported that life-threatening COVID-19 pneumonia was observed in people with mutations in genes previously associated with severe influenza. Mice with defective IFN-I pathway are more likely to die of influenza due to disproportionate inflammasome activation, not just because of high levels of viral replication. Probably, this may explain severe COVID-19 cases if IFN deficiency is presented. These genes that belong to the TLR3 and IFN-I signaling pathways were altered in 3.5% of the tested individuals, resulting in the incapability of producing or responding to IFN-I. Another study by Bastard *et al*[117] showed that a form of autoimmunity may contribute to viral infection susceptibility, such as autoantibodies to IFNs. People with autoimmune polyglandular syndrome type 1 were reported to developed severe COVID-19 pneumonia.

Anti-IFN-I autoantibodies have been found in various diseases. However, the underlying mechanisms for severe COVID-19 include uncontrolled viral replication and spread but also disruption of immune system function as suppression of inflammasome or enhanced cytokines production[118-120]. Regarding the gene cluster encoding antiviral restriction enzyme activators (OAS), they encode enzymes, producing a host antiviral mediator [2',5'-oligoadenylate (2-5A)]. The latter activates an effector enzyme RNase L which degrades double-stranded RNA[121]. Vietnamese and Chinese studies documented the OAS1 variants role in SARS-CoV susceptibility[122, 123]. Variants in chromosome 19p13.3 (rs2109069) that encodes DPP9 were clinically related to pulmonary fibrosis. DPP9 encodes a serine protease with important immune functions such as antigen presentation and inflammasome activation as well as cleavage of CXCL (a key antiviral signaling mediator)[124].

The association between *TYK2*, *CXCR6*, *CCR2*, and *CCR3* expression and severe COVID-19 was also demonstrated[24].

*CCR2* for monocyte chemoattractant protein-1 is expressed strongly in the lung tissues, promoting chemotaxis of monocytes and macrophages towards sites of inflammation. In critical COVID-19 patients on mechanical ventilation, *CCR2* is overexpressed and detectable in bronchoalveolar lavage fluid samples[125]. Moreover, circulating monocyte chemoattractant protein-1 amounts are related to a more serious disease[126].

Data on the candidate genes associated with severe COVID-19 are summarized in Table 1.

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## TRENDS IN THERAPEUTIC STRATEGIES AND THE GENETIC FACTORS SIGNIFICANCE

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In serious COVID-19, it is the lung inflammation that mainly leads to fatal outcomes. This is why many efforts were given to identify the possible host genetic variants associated with critical illness[127]. Evidence has shown that hospitalized patients differed significantly from those with mild or moderate diseases. Many distinct disorder phenotypes occur with different symptom patterns. Furthermore, they exhibit different responses to immunosuppressive treatment[114].

Some experts suggest that corticosteroid therapy is detrimental in patients with non-respiratory failure, although there are major benefits in patients with critical respiratory failure[113]. Hence, it is considered that different pathophysiologic mechanisms contribute to critical COVID-19 cases with respiratory failure.

Based on the possible genetic alterations harbored by the critically ill COVID-19 patients, some trends were observed regarding the treatment options. For example, individuals with IFN-I genetic mutations would benefit from interferon treatment, but such therapy would not be of any advantage to people who have *IFNAR* encoding gene mutations. Moreover, whether patients have IFN neutralizing antibodies, therapies such as IFN- $\beta$  or IFN- $\alpha$  in early infection may also be beneficial[115].

The *OAS* genes are also a potential therapeutic target. Inhibitors of endogenous phosphodiesterase 12 were shown to augment *OAS*-mediated antiviral activity[128]. In line with this, *TYK2* is one of the targets for janus kinase inhibitors (*i.e.*, baricitinib),

**Table 1 Summary of reported genome wide association studies between human genes and severe coronavirus disease 2019**

Gene(s)	Polymorphism(s) and genotypes	Chromosome location	Reported COVID-19 associations	Ref.
<i>SLC6A20, LZFTL1, CCR9, CXCR6, XCR1, and FYCO1</i>	Rs11385942-GA	3p21.31	Severe disease (respiratory problems)	[28]
<i>ABO</i>	rs657152	9q34.2	Higher risk of infection in blood group A and a protective effect in blood group O as compared with other blood groups	[37, 38]
<i>HLA</i>	a/HLA-B*15:03 and HLA-B*46:01; b/HLA-DBR*15:01 HLA-DQB*06:02 and HLA-B*27:07; c/ HLA-A*11:01, HLA-B*51:01 and HLA-C*14:02	6p21.33	Vulnerable to COVID-19 for HLA-B*46:01 and protective T-cell immunity for HLA-B*15:03 may predispose to a less favorable outcome and severe COVID-19; Preliminary results in the worst clinical outcome in China patients	[41]
<i>TMEM189-UBE2V1</i>	rs6020289-A	20q13.13	Severe disease	[42]
<i>ACE2</i>	p.Arg514-Gly	Xp22.2		[30]
<i>TMPRSS2</i>	p.Val160Met (rs12329760)	21q22.3	Severe disease, vulnerable to COVID-19 with risk factors	[29, 30]
<i>TLR7</i>	g.12905756_12905759del and g.12906010G>T	Xp22.2	Severe disease	[29]
<i>ApoE</i>	rs429358-C-C (e4e4)	19q13.32	Severe disease especially with dementia, cardiovascular disease and type 2 diabetes	[84, 85]
<i>IFITM3</i>	rs12252-C/C	11p15.5	Mild to moderate disease (with hospitalization)	[91, 94]
<i>CTSB, CTSL</i>		8p23.1, 9q21.33	Low frequencies; severe disease with cardiovascular conditions	[97, 100]
<i>PIEZO</i>	rs7184427, rs6500495 and rs7404939	16q24.3	Severe COVID-19 and fatality, independently of the risk factors	[101]
<i>OAS1, OAS2 and OAS3</i>	rs10735079	12q24.13	Severe COVID-19 and critical illness	[24]
<i>TYK2</i>	rs2109069	19p13.2	Critical illness	[24]
<i>DPP9</i>	rs2109069	19p13.3	Severe COVID-19; Idiopathic pulmonary fibrosis	[24]
<i>IFNAR2</i>	rs2236757	21q22.1	Severe COVID-19 and other viral diseases	[24]

COVID-19: Coronavirus disease 2019.

and anti-CCR2 has also shown safety for other diseases, such as rheumatoid disease. However, all these therapies could be called only experimental[129].

Immunosuppressive agents prescribed to patients with autoimmune diseases might have a beneficial effect on the COVID-19 course in these patients by reducing the risk of cytokine storm. Although we have made detailed literature research, sufficient evidence was not found.

Notwithstanding, the continuous search for appropriate therapy insists on further studies on the genetic factors, their contribution to severe COVID-19, as well as their potential role in the invention of effective treatment.

## CONCLUSION

GWAS contributes to understanding the genetic basis of COVID-19 and potential associations between the virus infection severity and specific gene loci. The global aim is to elucidate the molecular mechanisms and the optimizing of prevention and treatment of SARS-CoV-2 infection. In the last year, research on polymorphic variants or in proximity to the candidate genes has shown a strong, statistically significant association with the severity of the disease. Further study of genes and genetic variants will be of great benefit for the prevention and individual risk assessment and disease severity in different populations. These scientific data will serve as a basis for the development of clinically applicable diagnostic and prognostic tests for patients at

high risk of COVID-19.

However, GWAS has some limitations. The present data may not be fully comprehensive, as well as genotype-phenotype elaboration and corrections cannot be made for all conceivable causes of bias (e.g., cardiovascular and metabolic underlying factors contributing to COVID-19). Further studies regarding the genetic data are warranted, both in terms of their utility for the therapeutic risk profiling of COVID-19 patients and in terms of avoiding the mechanical knowledge of infection pathophysiology.

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