**Name of Journal:** *World Journal of Virology*

**Manuscript NO:** 65115

**Manuscript Type:** REVIEW

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

Kotsev SV *et al*. Genetics and severe COVID-19

Stanislav Vasilev Kotsev, Dimitrina Miteva, Stanislava Krayselska, Martina Shopova, Maria Pishmisheva-Peleva, Spaska Angelova Stanilova, Tsvetelina Velikova

**Stanislav Vasilev Kotsev, Martina Shopova, Maria Pishmisheva-Peleva,** Department of Infectious Diseases, Pazardzhik Multiprofile Hospital for Active Treatment, Pazardzhik 4400, Bulgaria

**Dimitrina Miteva,** Department of Genetics, Sofia University “St. Kliment Ohridski”, Sofia 1000, Bulgaria

**Stanislava Krayselska,** Private Practice General Praxis, Sofia 1113, Bulgaria

**Spaska Angelova Stanilova,** Department of Molecular Biology, Immunology and Medical Genetics, Medical Faculty, Trakia University, Stara Zagora 6000, Bulgaria

**Tsvetelina Velikova,** Department of Clinical Immunology, University Hospital Lozenetz, Sofia 1407, Bulgaria

**Tsvetelina Velikova,** Medical Faculty, Sofia University “St. Kliment Ohridski”, Sofia 1407, Bulgaria

**Author contributions:** All the authors wrote sections in the paper; all authors revised and approved the final version of the manuscript.

**Corresponding author: Tsvetelina Velikova, MD, PhD, Assistant Professor,** Department of Clinical Immunology, University Hospital Lozenetz, Kozyak 1 Street, Sofia 1407, Bulgaria. tsvelikova@medfac.mu-sofia.bg

**Received:** February 28, 2021

**Revised:** May 19, 2021

**Accepted:** May 23, 2021

**Published online:** July 25, 2021

**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*

**©The** **Author(s) 2021.** Published by Baishideng Publishing Group Inc. All rights reserved.

Kotsev SV, Miteva D, Krayselska S, Shopova M, Pishmisheva-Peleva M, Stanilova SA, Velikova T. Hypotheses and facts for genetic factors related to severe COVID-19. *World J Virol* 2021; 10(4): 137-155 URL: https://www.wjgnet.com/2220-3249/full/v10/i4/137.htm DOI: https://dx.doi.org/10.5501/wjv.v10.i4.137

**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.

**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.

**Main** **CONVENTIONAL RISK FACTORS FOR SEVERE COVID-19**

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.

**CHARACTERISTICS OF CRITICALLY ILL COVID-19 PATIENTS**

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].

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

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, LZTFL1, 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 3p21.31and rs657152 at locus 9q34.2. Leucine zipper transcription factor-like 1 (LZTFL1) might be the most important, with the rs11385942 variant. LZTFL1 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. А 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-α 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 197th 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 ε2, ε3, and ε4 alleles. The ApoE ε4 genotype is associated with dementia and delirium[85], and the ε4ε4 homozygous genotype are at a 14-fold increased risk of Alzheimer’s disease[86].

Using the United Kingdom Biobank data, associations between ApoE ε4 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 ε3 homozygotes[84,85]. The heterozygotes (ε3/ε4) are at lower risk.

If the ApoE ε4 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 ε4 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 IFTM3 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]. ARS-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***](https://www.allacronyms.com/piezo-type_mechanosensitive_ion_channel_component_1/abbreviated) ***(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 Ca2+, 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 Ca2+-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-α/β 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/](about:blank)) 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.

**TRENDS IN THERAPEUTIC STRATEGIES AND THE GENETIC FACTORS SIGNIFICANCE**

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-β or IFN-α 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), 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.

**REFERENCES**

1 **WHO**. Clinical management of COVID-19 interim guidance. [cited 27 May 2020]. Available from: https://www.who.int/publications/i/item/clinical-management-of-covid-19

2 **Novel Coronavirus Pneumonia Emergency Response Epidemiology Team**. Vital surveillances: the epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) – China. *China CDC Weekly* 2020; **2**: 113-122 [DOI: 10.46234/ccdcw2020.032]

3 **WHO.** COVID-19 Weekly Epidemiological Update. [cited 27 May 2020]. Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update---23-february-2021

4 **Zhou F**, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**: 1054-1062 [PMID: 32171076 DOI: 10.1016/S0140-6736(20)30566-3]

5 **Velikova TV**, Miteva L, Stanilov N, Spassova Z, Stanilova SA. Interleukin-6 compared to the other Th17/Treg related cytokines in inflammatory bowel disease and colorectal cancer. *World J Gastroenterol* 2020; **26**: 1912-1925 [PMID: 32390702 DOI: 10.3748/wjg.v26.i16.1912]

6 **Li X**, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. *J Pharm Anal* 2020; **10**: 102-108 [PMID: 32282863 DOI: 10.1016/j.jpha.2020.03.001]

7 **Malik P**, Patel U, Mehta D, Patel N, Kelkar R, Akrmah M, Gabrilove JL, Sacks H. Biomarkers and outcomes of COVID-19 hospitalisations: systematic review and meta-analysis. *BMJ Evid Based Med* 2021; **26**: 107-108 [PMID: 32934000 DOI: 10.1136/bmjebm-2020-111536]

8 **Chen G**, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, Zhang X, Zhang M, Wu S, Song J, Chen T, Han M, Li S, Luo X, Zhao J, Ning Q. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest* 2020; **130**: 2620-2629 [PMID: 32217835 DOI: 10.1172/JCI137244]

9 **Choudhary S**, Sreenivasulu K, Mitra P, Misra S, Sharma P. Role of Genetic Variants and Gene Expression in the Susceptibility and Severity of COVID-19. *Ann Lab Med* 2021; **41**: 129-138 [PMID: 33063674 DOI: 10.3343/alm.2021.41.2.129]

10 **Debnath M**, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. *FASEB J* 2020; **34**: 8787-8795 [PMID: 32525600 DOI: 10.1096/fj.202001115R]

11 **Matsushita K**, Ding N, Kou M, Hu X, Chen M, Gao Y, Honda Y, Zhao D, Dowdy D, Mok Y, Ishigami J, Appel LJ. The Relationship of COVID-19 Severity with Cardiovascular Disease and Its Traditional Risk Factors: A Systematic Review and Meta-Analysis. *Glob Heart* 2020; **15**: 64 [PMID: 33150129 DOI: 10.5334/gh.814]

12 **Jordan RE**, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. *BMJ* 2020; **368**: m1198 [PMID: 32217618 DOI: 10.1136/bmj.m1198]

13 **Gebhard C**, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. *Biol Sex Differ* 2020; **11**: 29 [PMID: 32450906 DOI: 10.1186/s13293-020-00304-9]

14 **Napolioni V**, Predazzi IM. Age- and gender-specific association between ADA (22G>A) and TNF-α (-308G>A) genetic polymorphisms. *Tissue Antigens* 2010; **76**: 311-314 [PMID: 20522203 DOI: 10.1111/j.1399-0039.2010.01510.x]

15 **Grigorova AA**, Trenova AG, Stanilova SA. Association of polymorphism -308G/A in tumor necrosis factor-alpha gene (TNF-α) and TNF-α serum levels in patients with relapsing-remitting multiple sclerosis. *Neurol Res* 2021; **43**: 291-298 [PMID: 33252003 DOI: 10.1080/01616412.2020.1853987]

16 **Miteva L**, Trenova A, Slavov G, Stanilova S. IL12B gene polymorphisms have sex-specific effects in relapsing-remitting multiple sclerosis. *Acta Neurol Belg* 2019; **119**: 83-93 [PMID: 30554348 DOI: 10.1007/s13760-018-01066-3]

17 **Guo W**, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020: e3319 [PMID: 32233013 DOI: 10.1002/dmrr.3319]

18 **Docherty AB**, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, Holden KA, Read JM, Dondelinger F, Carson G, Merson L, Lee J, Plotkin D, Sigfrid L, Halpin S, Jackson C, Gamble C, Horby PW, Nguyen-Van-Tam JS, Ho A, Russell CD, Dunning J, Openshaw PJ, Baillie JK, Semple MG; ISARIC4C investigators. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; **369**: m1985 [PMID: 32444460 DOI: 10.1136/bmj.m1985]

19 **Giamarellos-Bourboulis EJ**, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M, Kyriakopoulou M, Dimopoulos G, Koutsodimitropoulos I, Velissaris D, Koufargyris P, Karageorgos A, Katrini K, Lekakis V, Lupse M, Kotsaki A, Renieris G, Theodoulou D, Panou V, Koukaki E, Koulouris N, Gogos C, Koutsoukou A. Complex Immune Dysregulation in COVID-19 Patients with Severe Respiratory Failure. *Cell Host Microbe* 2020; **27**: 992-1000.e3 [PMID: 32320677 DOI: 10.1016/j.chom.2020.04.009]

20 **McGonagle D**, O'Donnell JS, Sharif K, Emery P, Bridgewood C. Immune mechanisms of pulmonary intravascular coagulopathy in COVID-19 pneumonia. *Lancet Rheumatol* 2020; **2**: e437-e445 [PMID: 32835247 DOI: 10.1016/S2665-9913(20)30121-1]

21 **Tsai PH**, Lai WY, Lin YY, Luo YH, Lin YT, Chen HK, Chen YM, Lai YC, Kuo LC, Chen SD, Chang KJ, Liu CH, Chang SC, Wang FD, Yang YP. Clinical manifestation and disease progression in COVID-19 infection. *J Chin Med Assoc* 2021; **84**: 3-8 [PMID: 33230062 DOI: 10.1097/JCMA.0000000000000463]

22 **Wu Z**, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. *JAMA* 2020; **323**: 1239-1242 [PMID: 32091533 DOI: 10.1001/jama.2020.2648]

23 **Wang D**, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. *JAMA* 2020; **323**: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

24 **Pairo-Castineira E**, Clohisey S, Klaric L, Bretherick AD, Rawlik K, Pasko D, Walker S, Parkinson N, Fourman MH, Russell CD, Furniss J, Richmond A, Gountouna E, Wrobel N, Harrison D, Wang B, Wu Y, Meynert A, Griffiths F, Oosthuyzen W, Kousathanas A, Moutsianas L, Yang Z, Zhai R, Zheng C, Grimes G, Beale R, Millar J, Shih B, Keating S, Zechner M, Haley C, Porteous DJ, Hayward C, Yang J, Knight J, Summers C, Shankar-Hari M, Klenerman P, Turtle L, Ho A, Moore SC, Hinds C, Horby P, Nichol A, Maslove D, Ling L, McAuley D, Montgomery H, Walsh T, Pereira AC, Renieri A; GenOMICC Investigators; ISARIC4C Investigators; COVID-19 Human Genetics Initiative; 23andMe Investigators; BRACOVID Investigators; Gen-COVID Investigators, Shen X, Ponting CP, Fawkes A, Tenesa A, Caulfield M, Scott R, Rowan K, Murphy L, Openshaw PJM, Semple MG, Law A, Vitart V, Wilson JF, Baillie JK. Genetic mechanisms of critical illness in COVID-19. *Nature* 2021; **591**: 92-98 [PMID: 33307546 DOI: 10.1038/s41586-020-03065-y]

25 **Jeng MJ**. Coronavirus disease 2019 in children: Current status. *J Chin Med Assoc* 2020; **83**: 527-533 [PMID: 32502117 DOI: 10.1097/JCMA.0000000000000323]

26 **Cruz AT**, Zeichner SL. COVID-19 in Children: Initial Characterization of the Pediatric Disease. *Pediatrics* 2020; **145** [PMID: 32179659 DOI: 10.1542/peds.2020-0834]

27 **Rhodes A**, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche JD, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC, Machado FR, Marini JJ, Marshall JC, Mazuski JE, McIntyre LA, McLean AS, Mehta S, Moreno RP, Myburgh J, Navalesi P, Nishida O, Osborn TM, Perner A, Plunkett CM, Ranieri M, Schorr CA, Seckel MA, Seymour CW, Shieh L, Shukri KA, Simpson SQ, Singer M, Thompson BT, Townsend SR, Van der Poll T, Vincent JL, Wiersinga WJ, Zimmerman JL, Dellinger RP. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017; **43**: 304-377 [PMID: 28101605 DOI: 10.1007/s00134-017-4683-6]

28 **Severe Covid-19 GWAS Group.**, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, Invernizzi P, Fernández J, Prati D, Baselli G, Asselta R, Grimsrud MM, Milani C, Aziz F, Kässens J, May S, Wendorff M, Wienbrandt L, Uellendahl-Werth F, Zheng T, Yi X, de Pablo R, Chercoles AG, Palom A, Garcia-Fernandez AE, Rodriguez-Frias F, Zanella A, Bandera A, Protti A, Aghemo A, Lleo A, Biondi A, Caballero-Garralda A, Gori A, Tanck A, Carreras Nolla A, Latiano A, Fracanzani AL, Peschuck A, Julià A, Pesenti A, Voza A, Jiménez D, Mateos B, Nafria Jimenez B, Quereda C, Paccapelo C, Gassner C, Angelini C, Cea C, Solier A, Pestaña D, Muñiz-Diaz E, Sandoval E, Paraboschi EM, Navas E, García Sánchez F, Ceriotti F, Martinelli-Boneschi F, Peyvandi F, Blasi F, Téllez L, Blanco-Grau A, Hemmrich-Stanisak G, Grasselli G, Costantino G, Cardamone G, Foti G, Aneli S, Kurihara H, ElAbd H, My I, Galván-Femenia I, Martín J, Erdmann J, Ferrusquía-Acosta J, Garcia-Etxebarria K, Izquierdo-Sanchez L, Bettini LR, Sumoy L, Terranova L, Moreira L, Santoro L, Scudeller L, Mesonero F, Roade L, Rühlemann MC, Schaefer M, Carrabba M, Riveiro-Barciela M, Figuera Basso ME, Valsecchi MG, Hernandez-Tejero M, Acosta-Herrera M, D'Angiò M, Baldini M, Cazzaniga M, Schulzky M, Cecconi M, Wittig M, Ciccarelli M, Rodríguez-Gandía M, Bocciolone M, Miozzo M, Montano N, Braun N, Sacchi N, Martínez N, Özer O, Palmieri O, Faverio P, Preatoni P, Bonfanti P, Omodei P, Tentorio P, Castro P, Rodrigues PM, Blandino Ortiz A, de Cid R, Ferrer R, Gualtierotti R, Nieto R, Goerg S, Badalamenti S, Marsal S, Matullo G, Pelusi S, Juzenas S, Aliberti S, Monzani V, Moreno V, Wesse T, Lenz TL, Pumarola T, Rimoldi V, Bosari S, Albrecht W, Peter W, Romero-Gómez M, D'Amato M, Duga S, Banales JM, Hov JR, Folseraas T, Valenti L, Franke A, Karlsen TH. Genomewide Association Study of Severe Covid-19 with Respiratory Failure. *N Engl J Med* 2020; **383**: 1522-1534 [PMID: 32558485 DOI: 10.1056/NEJMoa2020283]

29 **Anastassopoulou C**, Gkizarioti Z, Patrinos GP, Tsakris A. Human genetic factors associated with susceptibility to SARS-CoV-2 infection and COVID-19 disease severity. *Hum Genomics* 2020; **14**: 40 [PMID: 33092637 DOI: 10.1186/s40246-020-00290-4]

30 **Hou Y**, Zhao J, Martin W, Kallianpur A, Chung MK, Jehi L, Sharifi N, Erzurum S, Eng C, Cheng F. New insights into genetic susceptibility of COVID-19: an ACE2 and TMPRSS2 polymorphism analysis. *BMC Med* 2020; **18**: 216 [PMID: 32664879 DOI: 10.1186/s12916-020-01673-z]

31 **Vuille-dit-Bille RN**, Camargo SM, Emmenegger L, Sasse T, Kummer E, Jando J, Hamie QM, Meier CF, Hunziker S, Forras-Kaufmann Z, Kuyumcu S, Fox M, Schwizer W, Fried M, Lindenmeyer M, Götze O, Verrey F. Human intestine luminal ACE2 and amino acid transporter expression increased by ACE-inhibitors. *Amino Acids* 2015; **47**: 693-705 [PMID: 25534429 DOI: 10.1007/s00726-014-1889-6]

32 **Kuba K**, Imai Y, Ohto-Nakanishi T, Penninger JM. Trilogy of ACE2: a peptidase in the renin-angiotensin system, a SARS receptor, and a partner for amino acid transporters. *Pharmacol Ther* 2010; **128**: 119-128 [PMID: 20599443 DOI: 10.1016/j.pharmthera.2010.06.003]

33 **Wein AN**, McMaster SR, Takamura S, Dunbar PR, Cartwright EK, Hayward SL, McManus DT, Shimaoka T, Ueha S, Tsukui T, Masumoto T, Kurachi M, Matsushima K, Kohlmeier JE. CXCR6 regulates localization of tissue-resident memory CD8 T cells to the airways. *J Exp Med* 2019; **216**: 2748-2762 [PMID: 31558615 DOI: 10.1084/jem.20181308]

34 **Hickey MJ**, Held KS, Baum E, Gao JL, Murphy PM, Lane TE. CCR1 deficiency increases susceptibility to fatal coronavirus infection of the central nervous system. *Viral Immunol* 2007; **20**: 599-608 [PMID: 18158733 DOI: 10.1089/vim.2007.0056]

35 **Seo S**, Zhang Q, Bugge K, Breslow DK, Searby CC, Nachury MV, Sheffield VC. A novel protein LZTFL1 regulates ciliary trafficking of the BBSome and Smoothened. *PLoS Genet* 2011; **7**: e1002358 [PMID: 22072986 DOI: 10.1371/journal.pgen.1002358]

36 **Jiang H**, Promchan K, Lin BR, Lockett S, Chen D, Marshall H, Badralmaa Y, Natarajan V. LZTFL1 Upregulated by All-Trans Retinoic Acid during CD4+ T Cell Activation Enhances IL-5 Production. *J Immunol* 2016; **196**: 1081-1090 [PMID: 26700766 DOI: 10.4049/jimmunol.1500719]

37 **Wu Y**, Feng Z, Li P, Yu Q. Relationship between ABO blood group distribution and clinical characteristics in patients with COVID-19. *Clin Chim Acta* 2020; **509**: 220-223 [PMID: 32562665 DOI: 10.1016/j.cca.2020.06.026]

38 **Zhao J**, Yang Y, Huang H, Li D, Gu D, Lu X, Zhang Z, Liu L, Liu T, Liu Y, He Y, Sun B, Wei M, Yang G, Wang X, Zhang L, Zhou X, Xing M, Wang PG. Relationship between the ABO Blood Group and the COVID-19 Susceptibility. *Clin Infect Dis* 2020 [PMID: 32750119 DOI: 10.1093/cid/ciaa1150]

39 **Nguyen A**, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, Thompson RF. Human Leukocyte Antigen Susceptibility Map for Severe Acute Respiratory Syndrome Coronavirus 2. *J Virol* 2020; **94**: e00510-20 [PMID: 32303592 DOI: 10.1128/JVI.00510-20]

40 **Lin M**, Tseng HK, Trejaut JA, Lee HL, Loo JH, Chu CC, Chen PJ, Su YW, Lim KH, Tsai ZU, Lin RY, Lin RS, Huang CH. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet* 2003; **4**: 9 [PMID: 12969506 DOI: 10.1186/1471-2350-4-9]

41 **Novelli A**, Andreani M, Biancolella M, Liberatoscioli L, Passarelli C, Colona VL, Rogliani P, Leonardis F, Campana A, Carsetti R, Andreoni M, Bernardini S, Novelli G, Locatelli F. HLA allele frequencies and susceptibility to COVID-19 in a group of 99 Italian patients. *HLA* 2020; **96**: 610-614 [PMID: 32827207 DOI: 10.1111/tan.14047]

42 **Wang F**, Huang S, Gao R, Zhou Y, Lai C, Li Z, Xian W, Qian X, Li Z, Huang Y, Tang Q, Liu P, Chen R, Liu R, Li X, Tong X, Zhou X, Bai Y, Duan G, Zhang T, Xu X, Wang J, Yang H, Liu S, He Q, Jin X, Liu L. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. *Cell Discov* 2020; **6**: 83 [PMID: 33298875 DOI: 10.1038/s41421-020-00231-4]

43 **Thorsby E**, Lie BA. HLA associated genetic predisposition to autoimmune diseases: Genes involved and possible mechanisms. *Transpl Immunol* 2005; **14**: 175-182 [PMID: 15982560 DOI: 10.1016/j.trim.2005.03.021]

44 **Gough SC**, Simmonds MJ. The HLA Region and Autoimmune Disease: Associations and Mechanisms of Action. *Curr Genomics* 2007; **8**: 453-465 [PMID: 19412418 DOI: 10.2174/138920207783591690]

45 **Mahjoub S**, Mehri S, Ghazouani E, Ouarda F, Boussada R, Zaroui A, Mechmeche R, Hammami M, Ben Arab S. HLA class II polymorphisms in Tunisian patients with dilated cardiomyopathy. *Tissue Antigens* 2010; **75**: 679-683 [PMID: 20136773 DOI: 10.1111/j.1399-0039.2009.01432.x]

46 **Jiang X,** Coffee M, Bari A, Wang J, Jiang X, Huang J, Shi J, Dai J, Cai J, Zhang T, Wu Z, He G, Huang Y. Towards an artificial intelligence framework for data-driven prediction of coronavirus clinical severity. *Computers, Materials & Continua* 2020; **63**: 537-551 [DOI: 10.32604/cmc.2020.010691]

47 **Stelzer G**, Rosen N, Plaschkes I, Zimmerman S, Twik M, Fishilevich S, Stein TI, Nudel R, Lieder I, Mazor Y, Kaplan S, Dahary D, Warshawsky D, Guan-Golan Y, Kohn A, Rappaport N, Safran M, Lancet D. The GeneCards Suite: From Gene Data Mining to Disease Genome Sequence Analyses. *Curr Protoc Bioinformatics* 2016; **54**: 1.30.1-1.30.33 [PMID: 27322403 DOI: 10.1002/cpbi.5]

48 **Shi Y**, Wang Y, Shao C, Huang J, Gan J, Huang X, Bucci E, Piacentini M, Ippolito G, Melino G. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020; **27**: 1451-1454 [PMID: 32205856 DOI: 10.1038/s41418-020-0530-3]

49 **Millet JK**, Whittaker GR. Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. *Proc Natl Acad Sci U S A* 2014; **111**: 15214-15219 [PMID: 25288733 DOI: 10.1073/pnas.1407087111]

50 **Bertram S**, Dijkman R, Habjan M, Heurich A, Gierer S, Glowacka I, Welsch K, Winkler M, Schneider H, Hofmann-Winkler H, Thiel V, Pöhlmann S. TMPRSS2 activates the human coronavirus 229E for cathepsin-independent host cell entry and is expressed in viral target cells in the respiratory epithelium. *J Virol* 2013; **87**: 6150-6160 [PMID: 23536651 DOI: 10.1128/JVI.03372-12]

51 **Bhattacharyya C,** Das C, Ghosh A, Singh AK, Mukherjee S, Majumder PP. Global Spread of SARS-CoV-2 Subtype with Spike Protein Mutation D614G Is Shaped by Human Genomic Variations that Regulate Expression of TMPRSS2 and MX1 Genes. *bioRxiv* 2020 [DOI: 10.1101/2020.05.04.075911]

52 **Gierer S**, Bertram S, Kaup F, Wrensch F, Heurich A, Krämer-Kühl A, Welsch K, Winkler M, Meyer B, Drosten C, Dittmer U, von Hahn T, Simmons G, Hofmann H, Pöhlmann S. The spike protein of the emerging betacoronavirus EMC uses a novel coronavirus receptor for entry, can be activated by TMPRSS2, and is targeted by neutralizing antibodies. *J Virol* 2013; **87**: 5502-5511 [PMID: 23468491 DOI: 10.1128/JVI.00128-13]

53 **Shirogane Y**, Takeda M, Iwasaki M, Ishiguro N, Takeuchi H, Nakatsu Y, Tahara M, Kikuta H, Yanagi Y. Efficient multiplication of human metapneumovirus in Vero cells expressing the transmembrane serine protease TMPRSS2. *J Virol* 2008; **82**: 8942-8946 [PMID: 18562527 DOI: 10.1128/JVI.00676-08]

54 **Hoffmann M**, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; **181**: 271-280.e8 [PMID: 32142651 DOI: 10.1016/j.cell.2020.02.052]

55 **Zou X**, Chen K, Zou J, Han P, Hao J, Han Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Front Med* 2020; **14**: 185-192 [PMID: 32170560 DOI: 10.1007/s11684-020-0754-0]

56 **Qi F**, Qian S, Zhang S, Zhang Z. Single cell RNA sequencing of 13 human tissues identify cell types and receptors of human coronaviruses. *Biochem Biophys Res Commun* 2020; **526**: 135-140 [PMID: 32199615 DOI: 10.1016/j.bbrc.2020.03.044]

57 **Donoghue M**, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. *Circ Res* 2000; **87**: E1-9 [PMID: 10969042 DOI: 10.1161/01.res.87.5.e1]

58 **Glowacka I**, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, Steffen I, Tsegaye TS, He Y, Gnirss K, Niemeyer D, Schneider H, Drosten C, Pöhlmann S. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. *J Virol* 2011; **85**: 4122-4134 [PMID: 21325420 DOI: 10.1128/JVI.02232-10]

59 **Vaduganathan M**, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. *N Engl J Med* 2020; **382**: 1653-1659 [PMID: 32227760 DOI: 10.1056/NEJMsr2005760]

60 **Banu N**, Panikar SS, Leal LR, Leal AR. Protective role of ACE2 and its downregulation in SARS-CoV-2 infection leading to Macrophage Activation Syndrome: Therapeutic implications. *Life Sci* 2020; **256**: 117905 [PMID: 32504757 DOI: 10.1016/j.lfs.2020.117905]

61 **Patel VB**, Mori J, McLean BA, Basu R, Das SK, Ramprasath T, Parajuli N, Penninger JM, Grant MB, Lopaschuk GD, Oudit GY. ACE2 Deficiency Worsens Epicardial Adipose Tissue Inflammation and Cardiac Dysfunction in Response to Diet-Induced Obesity. *Diabetes* 2016; **65**: 85-95 [PMID: 26224885 DOI: 10.2337/db15-0399]

62 **Henry BM**, Vikse J, Benoit S, Favaloro EJ, Lippi G. Hyperinflammation and derangement of renin-angiotensin-aldosterone system in COVID-19: A novel hypothesis for clinically suspected hypercoagulopathy and microvascular immunothrombosis. *Clin Chim Acta* 2020; **507**: 167-173 [PMID: 32348783 DOI: 10.1016/j.cca.2020.04.027]

63 **Oladejo BO,** Adeboboye CF, Adebolu TT. Understanding the genetic determinant of severity in viral diseases: a case of SARS-Cov-2 infection. *Egypt J Med Hum Genet* 2020; **21**: 77 [DOI: 10.1186/s43042-020-00122-z]

64 **Marionneau S**, Airaud F, Bovin NV, Le Pendu J, Ruvoën-Clouet N. Influence of the combined ABO, FUT2, and FUT3 polymorphism on susceptibility to Norwalk virus attachment. *J Infect Dis* 2005; **192**: 1071-1077 [PMID: 16107962 DOI: 10.1086/432546]

65 **Gemmati D**, Bramanti B, Serino ML, Secchiero P, Zauli G, Tisato V. COVID-19 and Individual Genetic Susceptibility/Receptivity: Role of ACE1/ACE2 Genes, Immunity, Inflammation and Coagulation. Might the Double X-chromosome in Females Be Protective against SARS-CoV-2 Compared to the Single X-Chromosome in Males? *Int J Mol Sci* 2020; **21** [PMID: 32423094 DOI: 10.3390/ijms21103474]

66 **Cao Y**, Li L, Feng Z, Wan S, Huang P, Sun X, Wen F, Huang X, Ning G, Wang W. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-CoV-2) receptor ACE2 in different populations. *Cell Discov* 2020; **6**: 11 [PMID: 32133153 DOI: 10.1038/s41421-020-0147-1]

67 **Stopsack KH**, Mucci LA, Antonarakis ES, Nelson PS, Kantoff PW. *TMPRSS2* and COVID-19: Serendipity or Opportunity for Intervention? *Cancer Discov* 2020; **10**: 779-782 [PMID: 32276929 DOI: 10.1158/2159-8290.CD-20-0451]

68 **Lubieniecka JM**, Cheteri MK, Stanford JL, Ostrander EA. Met160Val polymorphism in the TRMPSS2 gene and risk of prostate cancer in a population-based case-control study. *Prostate* 2004; **59**: 357-359 [PMID: 15065083 DOI: 10.1002/pros.20005]

69 **Matsuyama S**, Nao N, Shirato K, Kawase M, Saito S, Takayama I, Nagata N, Sekizuka T, Katoh H, Kato F, Sakata M, Tahara M, Kutsuna S, Ohmagari N, Kuroda M, Suzuki T, Kageyama T, Takeda M. Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells. *Proc Natl Acad Sci U S A* 2020; **117**: 7001-7003 [PMID: 32165541 DOI: 10.1073/pnas.2002589117]

70 **Vargas-Alarcón G**, Posadas-Sánchez R, Ramírez-Bello J. Variability in genes related to SARS-CoV-2 entry into host cells (ACE2, TMPRSS2, TMPRSS11A, ELANE, and CTSL) and its potential use in association studies. *Life Sci* 2020; **260**: 118313 [PMID: 32835700 DOI: 10.1016/j.lfs.2020.118313]

71 **Sharma S,** Singh I, Haider S, Malik MdZ, Ponnusamy K, Rai E. ACE2 Homo-dimerization, Human genomic variants and interaction of host proteins explain high population specific differences in outcomes of COVID19. 2020; *bioRxiv* [DOI: 10.1101/2020.04.24.050534]

72 **Benetti E**, Tita R, Spiga O, Ciolfi A, Birolo G, Bruselles A, Doddato G, Giliberti A, Marconi C, Musacchia F, Pippucci T, Torella A, Trezza A, Valentino F, Baldassarri M, Brusco A, Asselta R, Bruttini M, Furini S, Seri M, Nigro V, Matullo G, Tartaglia M, Mari F; GEN-COVID Multicenter Study, Renieri A, Pinto AM. ACE2 gene variants may underlie interindividual variability and susceptibility to COVID-19 in the Italian population. *Eur J Hum Genet* 2020; **28**: 1602-1614 [PMID: 32681121 DOI: 10.1038/s41431-020-0691-z]

73 **Latini A**, Agolini E, Novelli A, Borgiani P, Giannini R, Gravina P, Smarrazzo A, Dauri M, Andreoni M, Rogliani P, Bernardini S, Helmer-Citterich M, Biancolella M, Novelli G. COVID-19 and Genetic Variants of Protein Involved in the SARS-CoV-2 Entry into the Host Cells. *Genes (Basel)* 2020; **11** [PMID: 32867305 DOI: 10.3390/genes11091010]

74 **Moreno-Eutimio MA**, López-Macías C, Pastelin-Palacios R. Bioinformatic analysis and identification of single-stranded RNA sequences recognized by TLR7/8 in the SARS-CoV-2, SARS-CoV, and MERS-CoV genomes. *Microbes Infect* 2020; **22**: 226-229 [PMID: 32361001 DOI: 10.1016/j.micinf.2020.04.009]

75 **Cervantes-Barragan L**, Züst R, Weber F, Spiegel M, Lang KS, Akira S, Thiel V, Ludewig B. Control of coronavirus infection through plasmacytoid dendritic-cell-derived type I interferon. *Blood* 2007; **109**: 1131-1137 [PMID: 16985170 DOI: 10.1182/blood-2006-05-023770]

76 **Channappanavar R**, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, Sompallae R, McCray PB Jr, Meyerholz DK, Perlman S. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. *J Clin Invest* 2019; **129**: 3625-3639 [PMID: 31355779 DOI: 10.1172/JCI126363]

77 **Jaillon S**, Berthenet K, Garlanda C. Sexual Dimorphism in Innate Immunity. *Clin Rev Allergy Immunol* 2019; **56**: 308-321 [PMID: 28963611 DOI: 10.1007/s12016-017-8648-x]

78 **Klein SL**, Marriott I, Fish EN. Sex-based differences in immune function and responses to vaccination. *Trans R Soc Trop Med Hyg* 2015; **109**: 9-15 [PMID: 25573105 DOI: 10.1093/trstmh/tru167]

79 **Cutolo M**, Capellino S, Sulli A, Serioli B, Secchi ME, Villaggio B, Straub RH. Estrogens and autoimmune diseases. *Ann N Y Acad Sci* 2006; **1089**: 538-547 [PMID: 17261796 DOI: 10.1196/annals.1386.043]

80 **Martin GM**. APOE alleles and lipophylic pathogens. *Neurobiol Aging* 1999; **20**: 441-443 [PMID: 10604437 DOI: 10.1016/s0197-4580(99)00078-0]

81 **Wozniak MA,** Itzhaki RF., Faragher EB, James MW, Ryder SD, Irving WL. Apolipoprotein E‐ϵ4 protects against severe liver disease caused by hepatitis C virus. *Hepatology* 2020; **36**: 456-463 [DOI: 10.1053/jhep.2002.34745]

82 **van Exel E**, Koopman JJE, Bodegom DV, Meij JJ, Knijff P, Ziem JB, Finch CE, Westendorp RGJ. Effect of APOE ε4 allele on survival and fertility in an adverse environment. *PLoS One* 2017; **12**: e0179497 [PMID: 28683096 DOI: 10.1371/journal.pone.0179497]

83 **Mitter SS**, Oriá RB, Kvalsund MP, Pamplona P, Joventino ES, Mota RM, Gonçalves DC, Patrick PD, Guerrant RL, Lima AA. Apolipoprotein E4 influences growth and cognitive responses to micronutrient supplementation in shantytown children from northeast Brazil. *Clinics (Sao Paulo)* 2012; **67**: 11-18 [PMID: 22249475 DOI: 10.6061/clinics/2012(01)03]

84 **Kuo CL**, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, Melzer D. APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort. *J Gerontol A Biol Sci Med Sci* 2020; **75**: 2231-2232 [PMID: 32451547 DOI: 10.1093/gerona/glaa131]

85 **Kuo CL**, Pilling LC, Atkins JL, Kuchel GA, Melzer D. *ApoE* e2 and aging-related outcomes in 379,000 UK Biobank participants. *Aging (Albany NY)* 2020; **12**: 12222-12233 [PMID: 32511104 DOI: 10.18632/aging.103405]

86 **Farrer LA**, Cupples LA, Haines JL, Hyman B, Kukull WA, Mayeux R, Myers RH, Pericak-Vance MA, Risch N, van Duijn CM. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997; **278**: 1349-1356 [PMID: 9343467 DOI: 10.1001/jama.1997.03550160069041]

87 **Borenstein AR**, Mortimer JA, Wu Y, Jureidini-Webb FM, Fallin MD, Small BJ, Mullan M, Crawford FC. Apolipoprotein E and cognition in community-based samples of African Americans and Caucasians. *Ethn Dis* 2006; **16**: 9-15 [PMID: 16599342]

88 **Holmes L Jr**, Enwere M, Williams J, Ogundele B, Chavan P, Piccoli T, Chinacherem C, Comeaux C, Pelaez L, Okundaye O, Stalnaker L, Kalle F, Deepika K, Philipcien G, Poleon M, Ogungbade G, Elmi H, John V, Dabney KW. Black-White Risk Differentials in COVID-19 (SARS-COV2) Transmission, Mortality and Case Fatality in the United States: Translational Epidemiologic Perspective and Challenges. *Int J Environ Res Public Health* 2020; **17** [PMID: 32560363 DOI: 10.3390/ijerph17124322]

89 **Yánez DC**, Ross S, Crompton T. The IFITM protein family in adaptive immunity. *Immunology* 2020; **159**: 365-372 [PMID: 31792954 DOI: 10.1111/imm.13163]

90 **Zhang Y**, Makvandi-Nejad S, Qin L, Zhao Y, Zhang T, Wang L, Repapi E, Taylor S, McMichael A, Li N, Dong T, Wu H. Interferon-induced transmembrane protein-3 rs12252-C is associated with rapid progression of acute HIV-1 infection in Chinese MSM cohort. *AIDS* 2015; **29**: 889-894 [PMID: 25784441 DOI: 10.1097/QAD.0000000000000632]

91 **Thevarajan I**, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, Jia X, Nicholson S, Catton M, Cowie B, Tong SYC, Lewin SR, Kedzierska K. Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. *Nat Med* 2020; **26**: 453-455 [PMID: 32284614 DOI: 10.1038/s41591-020-0819-2]

92 **Wang Z**, Zhang A, Wan Y, Liu X, Qiu C, Xi X, Ren Y, Wang J, Dong Y, Bao M, Li L, Zhou M, Yuan S, Sun J, Zhu Z, Chen L, Li Q, Zhang Z, Zhang X, Lu S, Doherty PC, Kedzierska K, Xu J. Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection. *Proc Natl Acad Sci U S A* 2014; **111**: 769-774 [PMID: 24367104 DOI: 10.1073/pnas.1321748111]

93 **Gómez J**, Albaiceta GM, Cuesta-Llavona E, García-Clemente M, López-Larrea C, Amado-Rodríguez L, López-Alonso I, Melón S, Alvarez-Argüelles ME, Gil-Peña H, Vidal-Castiñeira JR, Corte-Iglesias V, Saiz ML, Alvarez V, Coto E. The Interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 C variant is associated with COVID-19. *Cytokine* 2021; **137**: 155354 [PMID: 33113474 DOI: 10.1016/j.cyto.2020.155354]

94 **Zhang Y**, Qin L, Zhao Y, Zhang P, Xu B, Li K, Liang L, Zhang C, Dai Y, Feng Y, Sun J, Hu Z, Xiang H, Knight JC, Dong T, Jin R. Interferon-Induced Transmembrane Protein 3 Genetic Variant rs12252-C Associated With Disease Severity in Coronavirus Disease 2019. *J Infect Dis* 2020; **222**: 34-37 [PMID: 32348495 DOI: 10.1093/infdis/jiaa224]

95 **Zhou P**, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, Si HR, Zhu Y, Li B, Huang CL, Chen HD, Chen J, Luo Y, Guo H, Jiang RD, Liu MQ, Chen Y, Shen XR, Wang X, Zheng XS, Zhao K, Chen QJ, Deng F, Liu LL, Yan B, Zhan FX, Wang YY, Xiao GF, Shi ZL. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 2020; **579**: 270-273 [PMID: 32015507 DOI: 10.1038/s41586-020-2012-7]

96 **Sungnak W**, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, Talavera-López C, Maatz H, Reichart D, Sampaziotis F, Worlock KB, Yoshida M, Barnes JL; HCA Lung Biological Network. SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. *Nat Med* 2020; **26**: 681-687 [PMID: 32327758 DOI: 10.1038/s41591-020-0868-6]

97 **Lee IH**, Lee JW, Kong SW. A survey of genetic variants in SARS-CoV-2 interacting domains of ACE2, TMPRSS2 and TLR3/7/8 across populations. *Infect Genet Evol* 2020; **85**: 104507 [PMID: 32858233 DOI: 10.1016/j.meegid.2020.104507]

98 **Kang Y**, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, Chen Y, Han Y. Cardiovascular manifestations and treatment considerations in COVID-19. *Heart* 2020; **106**: 1132-1141 [PMID: 32354800 DOI: 10.1136/heartjnl-2020-317056]

99 **Akhmerov A**, Marbán E. COVID-19 and the Heart. *Circ Res* 2020; **126**: 1443-1455 [PMID: 32252591 DOI: 10.1161/CIRCRESAHA.120.317055]

100 **Yang J**, Chen T, Zhou Y. Mediators of SARS-CoV-2 entry are preferentially enriched in cardiomyocytes. *Hereditas* 2021; **158**: 4 [PMID: 33397514 DOI: 10.1186/s41065-020-00168-4]

101 **Cheng CW,** Deivasikamani V, Ludlow MJ, De Vecchis D, Kalli AC, Beech DJ, Sukuma P. Genetic variants of PIEZO1 associate with COVID-19 fatality. *MedRvix* 2020 [DOI: 10.1101/2020.06.01.20119651]

102 **Greber UF**. Virus and Host Mechanics Support Membrane Penetration and Cell Entry. *J Virol* 2016; **90**: 3802-3805 [PMID: 26842477 DOI: 10.1128/JVI.02568-15]

103 **de Armas-Rillo L**, Valera MS, Marrero-Hernández S, Valenzuela-Fernández A. Membrane dynamics associated with viral infection. *Rev Med Virol* 2016; **26**: 146-160 [PMID: 26817660 DOI: 10.1002/rmv.1872]

104 **Doñate-Macián P**, Jungfleisch J, Pérez-Vilaró G, Rubio-Moscardo F, Perálvarez-Marín A, Diez J, Valverde MA. The TRPV4 channel links calcium influx to DDX3X activity and viral infectivity. *Nat Commun* 2018; **9**: 2307 [PMID: 29899501 DOI: 10.1038/s41467-018-04776-7]

105 **Hover S**, Foster B, Barr JN, Mankouri J. Viral dependence on cellular ion channels - an emerging anti-viral target? *J Gen Virol* 2017; **98**: 345-351 [PMID: 28113044 DOI: 10.1099/jgv.0.000712]

106 **Straus MR**, Tang T, Lai AL, Flegel A, Bidon M, Freed JH, Daniel S, Whittaker GR. Ca2+ Ions Promote Fusion of Middle East Respiratory Syndrome Coronavirus with Host Cells and Increase Infectivity. *J Virol* 2020; **94** [PMID: 32295925 DOI: 10.1128/JVI.00426-20]

107 **Lai AL**, Millet JK, Daniel S, Freed JH, Whittaker GR. The SARS-CoV Fusion Peptide Forms an Extended Bipartite Fusion Platform that Perturbs Membrane Order in a Calcium-Dependent Manner. *J Mol Biol* 2017; **429**: 3875-3892 [PMID: 29056462 DOI: 10.1016/j.jmb.2017.10.017]

108 **Li J**, Hou B, Tumova S, Muraki K, Bruns A, Ludlow MJ, Sedo A, Hyman AJ, McKeown L, Young RS, Yuldasheva NY, Majeed Y, Wilson LA, Rode B, Bailey MA, Kim HR, Fu Z, Carter DA, Bilton J, Imrie H, Ajuh P, Dear TN, Cubbon RM, Kearney MT, Prasad RK, Evans PC, Ainscough JF, Beech DJ. Piezo1 integration of vascular architecture with physiological force. *Nature* 2014; **515**: 279-282 [PMID: 25119035 DOI: 10.1038/nature13701]

109 **Chong J,** De Vecchis D, Hyman AJ, Povstyan OV, Shi J, Beech DJ, Kalli AC. Computational reconstruction of the complete Piezo1 structure reveals a unique footprint and specific lipid interactions. *BioRxiv* 2017 [DOI: 10.1101/783753]

110 **Cummings MJ**, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, Aaron JG, Claassen J, Rabbani LE, Hastie J, Hochman BR, Salazar-Schicchi J, Yip NH, Brodie D, O'Donnell MR. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet* 2020; **395**: 1763-1770 [PMID: 32442528 DOI: 10.1016/S0140-6736(20)31189-2]

111 **The Recovery Collaborative Group**. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

112 **Sadler AJ**, Williams BR. Interferon-inducible antiviral effectors. *Nat Rev Immunol* 2008; **8**: 559-568 [PMID: 18575461 DOI: 10.1038/nri2314]

113 **Duncan CJ**, Mohamad SM, Young DF, Skelton AJ, Leahy TR, Munday DC, Butler KM, Morfopoulou S, Brown JR, Hubank M, Connell J, Gavin PJ, McMahon C, Dempsey E, Lynch NE, Jacques TS, Valappil M, Cant AJ, Breuer J, Engelhardt KR, Randall RE, Hambleton S. Human IFNAR2 deficiency: Lessons for antiviral immunity. *Sci Transl Med* 2015; **7**: 307ra154 [PMID: 26424569 DOI: 10.1126/scitranslmed.aac4227]

114 **WHO Solidarity Trial Consortium.**, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med* 2021; **384**: 497-511 [PMID: 33264556 DOI: 10.1056/NEJMoa2023184]

115 **Meffre E**, Iwasaki A. Interferon deficiency can lead to severe COVID. *Nature* 2020; **587**: 374-376 [PMID: 33139913 DOI: 10.1038/d41586-020-03070-1]

116 **Zhang Q**, Bastard P, Liu Z, Le Pen J, Moncada-Velez M, Chen J, Ogishi M, Sabli IKD, Hodeib S, Korol C, Rosain J, Bilguvar K, Ye J, Bolze A, Bigio B, Yang R, Arias AA, Zhou Q, Zhang Y, Onodi F, Korniotis S, Karpf L, Philippot Q, Chbihi M, Bonnet-Madin L, Dorgham K, Smith N, Schneider WM, Razooky BS, Hoffmann HH, Michailidis E, Moens L, Han JE, Lorenzo L, Bizien L, Meade P, Neehus AL, Ugurbil AC, Corneau A, Kerner G, Zhang P, Rapaport F, Seeleuthner Y, Manry J, Masson C, Schmitt Y, Schlüter A, Le Voyer T, Khan T, Li J, Fellay J, Roussel L, Shahrooei M, Alosaimi MF, Mansouri D, Al-Saud H, Al-Mulla F, Almourfi F, Al-Muhsen SZ, Alsohime F, Al Turki S, Hasanato R, van de Beek D, Biondi A, Bettini LR, D'Angio' M, Bonfanti P, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Oler AJ, Tompkins MF, Alba C, Vandernoot I, Goffard JC, Smits G, Migeotte I, Haerynck F, Soler-Palacin P, Martin-Nalda A, Colobran R, Morange PE, Keles S, Çölkesen F, Ozcelik T, Yasar KK, Senoglu S, Karabela ŞN, Rodríguez-Gallego C, Novelli G, Hraiech S, Tandjaoui-Lambiotte Y, Duval X, Laouénan C; COVID-STORM Clinicians; COVID Clinicians; Imagine COVID Group; French COVID Cohort Study Group; CoV-Contact Cohort; Amsterdam UMC Covid-19 Biobank; COVID Human Genetic Effort; NIAID-USUHS/TAGC COVID Immunity Group, Snow AL, Dalgard CL, Milner JD, Vinh DC, Mogensen TH, Marr N, Spaan AN, Boisson B, Boisson-Dupuis S, Bustamante J, Puel A, Ciancanelli MJ, Meyts I, Maniatis T, Soumelis V, Amara A, Nussenzweig M, García-Sastre A, Krammer F, Pujol A, Duffy D, Lifton RP, Zhang SY, Gorochov G, Béziat V, Jouanguy E, Sancho-Shimizu V, Rice CM, Abel L, Notarangelo LD, Cobat A, Su HC, Casanova JL. Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* 2020; **370** [PMID: 32972995 DOI: 10.1126/science.abd4570]

117 **Bastard P**, Rosen LB, Zhang Q, Michailidis E, Hoffmann HH, Zhang Y, Dorgham K, Philippot Q, Rosain J, Béziat V, Manry J, Shaw E, Haljasmägi L, Peterson P, Lorenzo L, Bizien L, Trouillet-Assant S, Dobbs K, de Jesus AA, Belot A, Kallaste A, Catherinot E, Tandjaoui-Lambiotte Y, Le Pen J, Kerner G, Bigio B, Seeleuthner Y, Yang R, Bolze A, Spaan AN, Delmonte OM, Abers MS, Aiuti A, Casari G, Lampasona V, Piemonti L, Ciceri F, Bilguvar K, Lifton RP, Vasse M, Smadja DM, Migaud M, Hadjadj J, Terrier B, Duffy D, Quintana-Murci L, van de Beek D, Roussel L, Vinh DC, Tangye SG, Haerynck F, Dalmau D, Martinez-Picado J, Brodin P, Nussenzweig MC, Boisson-Dupuis S, Rodríguez-Gallego C, Vogt G, Mogensen TH, Oler AJ, Gu J, Burbelo PD, Cohen JI, Biondi A, Bettini LR, D'Angio M, Bonfanti P, Rossignol P, Mayaux J, Rieux-Laucat F, Husebye ES, Fusco F, Ursini MV, Imberti L, Sottini A, Paghera S, Quiros-Roldan E, Rossi C, Castagnoli R, Montagna D, Licari A, Marseglia GL, Duval X, Ghosn J; HGID Lab; NIAID-USUHS Immune Response to COVID Group; COVID Clinicians; COVID-STORM Clinicians; Imagine COVID Group; French COVID Cohort Study Group; Milieu Intérieur Consortium; CoV-Contact Cohort; Amsterdam UMC Covid-19 Biobank; COVID Human Genetic Effort, Tsang JS, Goldbach-Mansky R, Kisand K, Lionakis MS, Puel A, Zhang SY, Holland SM, Gorochov G, Jouanguy E, Rice CM, Cobat A, Notarangelo LD, Abel L, Su HC, Casanova JL. Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; **370** [PMID: 32972996 DOI: 10.1126/science.abd4585]

118 **Pillai PS**, Molony RD, Martinod K, Dong H, Pang IK, Tal MC, Solis AG, Bielecki P, Mohanty S, Trentalange M, Homer RJ, Flavell RA, Wagner DD, Montgomery RR, Shaw AC, Staeheli P, Iwasaki A. Mx1 reveals innate pathways to antiviral resistance and lethal influenza disease. *Science* 2016; **352**: 463-466 [PMID: 27102485 DOI: 10.1126/science.aaf3926]

119 **Beccuti G**, Ghizzoni L, Cambria V, Codullo V, Sacchi P, Lovati E, Mongodi S, Iotti GA, Mojoli F. A COVID-19 pneumonia case report of autoimmune polyendocrine syndrome type 1 in Lombardy, Italy: letter to the editor. *J Endocrinol Invest* 2020; **43**: 1175-1177 [PMID: 32519200 DOI: 10.1007/s40618-020-01323-4]

120 **Guarda G**, Braun M, Staehli F, Tardivel A, Mattmann C, Förster I, Farlik M, Decker T, Du Pasquier RA, Romero P, Tschopp J. Type I interferon inhibits interleukin-1 production and inflammasome activation. *Immunity* 2011; **34**: 213-223 [PMID: 21349431 DOI: 10.1016/j.immuni.2011.02.006]

121 **Choi UY**, Kang JS, Hwang YS, Kim YJ. Oligoadenylate synthase-like (OASL) proteins: dual functions and associations with diseases. *Exp Mol Med* 2015; **47**: e144 [PMID: 25744296 DOI: 10.1038/emm.2014.110]

122 **Hamano E**, Hijikata M, Itoyama S, Quy T, Phi NC, Long HT, Ha LD, Ban VV, Matsushita I, Yanai H, Kirikae F, Kirikae T, Kuratsuji T, Sasazuki T, Keicho N. Polymorphisms of interferon-inducible genes OAS-1 and MxA associated with SARS in the Vietnamese population. *Biochem Biophys Res Commun* 2005; **329**: 1234-1239 [PMID: 15766558 DOI: 10.1016/j.bbrc.2005.02.101]

123 **He J**, Feng D, de Vlas SJ, Wang H, Fontanet A, Zhang P, Plancoulaine S, Tang F, Zhan L, Yang H, Wang T, Richardus JH, Habbema JD, Cao W. Association of SARS susceptibility with single nucleic acid polymorphisms of OAS1 and MxA genes: a case-control study. *BMC Infect Dis* 2006; **6**: 106 [PMID: 16824203 DOI: 10.1186/1471-2334-6-106]

124 **Zhang H**, Maqsudi S, Rainczuk A, Duffield N, Lawrence J, Keane FM, Justa-Schuch D, Geiss-Friedlander R, Gorrell MD, Stephens AN. Identification of novel dipeptidyl peptidase 9 substrates by two-dimensional differential in-gel electrophoresis. *FEBS J* 2015; **282**: 3737-3757 [PMID: 26175140 DOI: 10.1111/febs.13371]

125 **Zhou Z**, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S, Yang D, Zhang G, Li H, Chen F, Xu Y, Chen M, Gao Z, Yang J, Dong J, Liu B, Zhang X, Wang W, He K, Jin Q, Li M, Wang J. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. *Cell Host Microbe* 2020; **27**: 883-890.e2 [PMID: 32407669 DOI: 10.1016/j.chom.2020.04.017]

126 **Zhao Y**, Qin L, Zhang P, Li K, Liang L, Sun J, Xu B, Dai Y, Li X, Zhang C, Peng Y, Feng Y, Li A, Hu Z, Xiang H, Ogg G, Ho LP, McMichael A, Jin R, Knight JC, Dong T, Zhang Y. Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. *JCI Insight* 2020; **5** [PMID: 32501293 DOI: 10.1172/jci.insight.139834]

127 **Dorward DA**, Russell CD, Um IH, Elshani M, Armstrong SD, Penrice-Randal R, Millar T, Lerpiniere CEB, Tagliavini G, Hartley CS, Randle NP, Gachanja NN, Potey PMD, Dong X, Anderson AM, Campbell VL, Duguid AJ, Al Qsous W, BouHaidar R, Baillie JK, Dhaliwal K, Wallace WA, Bellamy COC, Prost S, Smith C, Hiscox JA, Harrison DJ, Lucas CD. Tissue-Specific Immunopathology in Fatal COVID-19. *Am J Respir Crit Care Med* 2021; **203**: 192-201 [PMID: 33217246 DOI: 10.1164/rccm.202008-3265OC]

128 **Wood ER**, Bledsoe R, Chai J, Daka P, Deng H, Ding Y, Harris-Gurley S, Kryn LH, Nartey E, Nichols J, Nolte RT, Prabhu N, Rise C, Sheahan T, Shotwell JB, Smith D, Tai V, Taylor JD, Tomberlin G, Wang L, Wisely B, You S, Xia B, Dickson H. The Role of Phosphodiesterase 12 (PDE12) as a Negative Regulator of the Innate Immune Response and the Discovery of Antiviral Inhibitors. *J Biol Chem* 2015; **290**: 19681-19696 [PMID: 26055709 DOI: 10.1074/jbc.M115.653113]

129 **Nguyen DT**, Mathias S, Bologa C, Brunak S, Fernandez N, Gaulton A, Hersey A, Holmes J, Jensen LJ, Karlsson A, Liu G, Ma'ayan A, Mandava G, Mani S, Mehta S, Overington J, Patel J, Rouillard AD, Schürer S, Sheils T, Simeonov A, Sklar LA, Southall N, Ursu O, Vidovic D, Waller A, Yang J, Jadhav A, Oprea TI, Guha R. Pharos: Collating protein information to shed light on the druggable genome. *Nucleic Acids Res* 2017; **45**: D995-D1002 [PMID: 27903890 DOI: 10.1093/nar/gkw1072]

**Footnotes**

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Invited manuscript

**Peer-review started:** February 28, 2021

**First decision:** May 5, 2021

**Article in press:** May 23, 2021

**Specialty type:** Infectious diseases

**Country/Territory of origin:** Bulgaria

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Gennaro RD **S-Editor:** Zhang H **L-Editor:** Filipodia **P-Editor:** Li JH

**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.** |
| *SLC6A20, LZFTL1, CCR9, CXCR6, XCR1, and FYCO1* | Rs11385942-GA | 3p21.31 | Severe disease (respiratory problems) | [28] |
| *ABO* | 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] |
| *HLA* | 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] |
| *TMEM189-UBE2V1* | rs6020289-A | 20q13.13 | Severe disease | [42] |
| *ACE2* | p.Arg514-Gly | Xp22.2 |  | [30] |
| *TMPRSS2* | p.Val160Met (rs12329760) | 21q22.3 | Severe disease, vulnerable to COVID-19 with risk factors | [29,30] |
| *TLR7* | g.12905756\_12905759del and g.12906010G>T | Xp22.2 | Severe disease | [29] |
| *ApoE* | rs429358-C-C (e4e4) | 19q13.32 | Severe disease especially with dementia, cardiovascular disease and type 2 diabetes | [84,85] |
| *IFITM3* | rs12252-C/C | 11p15.5 | Mild to moderate disease (with hospitalization) | [91,94] |
| *CTSB, CTSL* |  | 8p23.1, 9q21.33 | Low frequencies; severe disease with cardiovascular conditions | [97,100] |
| *PIEZO* | rs7184427, rs6500495 and rs7404939 | 16q24.3 | Severe COVID-19 and fatality, independently of the risk factors | [101] |
| *OAS1, OAS2 and OAS3* | rs10735079 | 12q24.13 | Severe COVID-19 and critical illness | [24] |
| *TYK2* | rs2109069 | 19p13.2 | Critical illness | [24] |
| *DPP9* | rs2109069 | 19p13.3 | Severe COVID-19; Idiopathic pulmonary fibrosis | [24] |
| *IFNAR2* | rs2236757 | 21q22.1 | Severe COVID-19 and other viral diseases | [24] |

COVID-19: Coronavirus disease 2019.



Published by **Baishideng Publishing Group Inc**

7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

**Telephone:** +1-925-3991568

**E-mail:** bpgoffice@wjgnet.com

**Help Desk:** https://www.f6publishing.com/helpdesk

https://www.wjgnet.com



**© 2021 Baishideng Publishing Group Inc. All rights reserved.**