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Review Article

Genetic Susceptibility to Severe Forms of COVID-19: What we learned in 2022

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Abstract

Host genetics of COVID-19 patients is constantly evolving and may play an important role in the management of hospitalized patients and the identification of new biomarkers. In 2022, numerous studies have been published examining genetic factors that may be associated with severe outcomes of COVID-19 disease, as well as different genetic biomarkers have been suggested for early diagnosis of severe SARS-CoV-2 infection. In this literature review, we provide relevant updated analyses, examining studies published in 2022 in the literature that correlate with what was published in previous years and that focused on host genetics in patients with severe or fatal forms of COVID-19, Studies using different genotyping and sequencing techniques for the identification of genetic polymorphisms with promising results on different genes of the Renin angiotensin system, Interferon system, ABO system, Apolipoprotein E, Dipeptidyl petptidase, Leucine Zipper Transcription Factor-Like Protein 1(LZTFL1) and HLA system in diverse populations.

Keywords: Genetic susceptibility, severe COVID-19, genotyping, sequencing.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by a novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), identified on December 12, 2019 in Wuhan City, Hubei Province, China (Lu *et al*., 2020) (Coronaviridae Study Group of the International Committee on Taxonomy of Viruses, 2020). The infection has rapidly spread to several countries around the world causing considerable morbidity and mortality, prompting the World Health Organization (WHO) to officially declare a global pandemic on March 11, 2020 (Dhama *et al*., 2020). The most common clinical manifestations of COVID-19 vary between individuals and populations from no or mild symptoms; fever, cough, dyspnea, headache, myalgia, arthralgia, asthenia and/or flu-like syndrome, to rapid progression to severe acute respiratory syndrome and multi-visceral failure leading to death (Bonny *et al*., 2020). Numerous clinical and experimental studies have identified risk factors associated with severe forms of COVID 19, including age, gender, and other comorbidities. Indeed, patients over 75 years of age present a high percentage of severe and critical forms (Feng *et al.*, 2020). Gender in turn plays a major role with a similar SARS-CoV-2 infection rate for both sexes, but with a 1.7 higher case fatality rate in men (Niederman *et al.*, 2020; Scully *et al*., 2020). As for other comorbidities, cardiovascular disease, diabetes, chronic respiratory disease and cancer were all associated with high percentages of critical forms according to the Chinese Center for Disease Control and Prevention (Jordan *et al*., 2020; Wu & McGoogan, 2020). Obesity and smoking have also been reported in the literature (R. Huang *et al*., 2020). However, all these factors do not explain the severity of COVID-19 in young patients with no medical and surgical history.

COVID-19 is a multifactorial pathology in which environmental, social, clinical, and genetic factors influence the outcome and progression of the disease (Docherty *et al*., 2020). However, interest in the genetics of the SARS-CoV-2 infected host is growing steadily, and large-scale genomic studies have

demonstrated numerous genetic determinants conditioning the variability of the response to this infection (Barmania *et al*., 2022). The aim of this work is to highlight the most relevant host genetic polymorphisms and biomarkers correlated with severe forms of COVID-19 that have been identified or re-studied in 2022. Knowledge of the association between host genetics and the severity of COVID-19 allows us to improve the management of patients with severe forms of SARS-CoV-2 infection and make an early diagnosis of patients susceptible to complications through identified genetic biomarkers.

Renin Angiotensin System:

Angiotensine-converting enzyme (ACE 1):

The main pathway of entry of the virus remains the first candidate of genetic determinants. Indeed, the Renin Angiotensin System (RAA), which binds to SARS-CoV-2 and facilitates its entry into the host cell, plays an important role in the pathogenesis of COVID-19, ACE1catalyzes the synthesis of angiotensin-II (Ang-II) from Ang-I, and ACE2 hydrolyzes Ang-II to Ang-1-7. Intron 16 of the human ACE1 gene on chromosome 17 contains an insertion (I) or a deletion (D), this ACE I / D polymorphism determines the plasma concentration of ACE being approximately doubled in individuals with the DD genotype compared to individuals II, with ID individuals having intermediate concentrations (Dai *et al*., 2019) . A study including 26 critical COVID 19 patients with severe respiratory failure (paO2/FiO2<100) admitted to intensive care unit (ICU) in Italy demonstrated an association between ACE 1 DD genotype (73%) and morbidity and mortality risk of COVID 19 (Annunziata *et al.*, 2021). The same conclusion was reached in a recent study by Halim Saad and his team who studied 387 patients and also associated by genotyping tests the ACE 1 DD polymorphism and D allele with severe forms of COVID 19 (p= 0.026 and p=0.014 respectively) (Saad *et al*., 2021). Another study involving the ACE I/D polymorphism in COVID-19 disease complicated by pulmonary embolism was carried out in Italy, the evaluation showed a high prevalence of the homozygous D/D polymorphism in critical COVID 19 patients hospitalized in the ICU and presenting pulmonary embolisms (PE) (46%) confirmed by CT scan (p=0.048). Noted that there was no difference in D-Dimer levels between patients with and without PE, however, the increase in C-reactive protein (CRP) observed in patients with PE suggests the important role of inflammation in the pathogenesis of thrombotic complications in patients infected with SARS-CoV-2 (Calabrese *et al*., 2021). The activities of angiotensin-converting enzyme ACE1 and ACE2 in COVID-19 disease may be crucially involved in the thrombo-inflammatory process.

Angiotensine-converting enzyme 2 (ACE 2):

SARS-CoV-2 binds to ACE2 as a cellular entry receptor via the S1 subunit of the viral S protein in the receptor binding domain (RBD), fusion of cellular and viral membranes is dependent on cleavage of the S protein by the host cell proteases FURIN and TMPRSS2 (The Serine Transmembrane Protease 2) at the S1/S2 and S2' site respectively, resulting in activation of the S protein (Hoffmann *et al*., 2020). An in silico study evolving ACE2 polymorphisms in a cohort of 290,000 samples from different populations identified natural variants that increase host susceptibility to infection, including S19P , I21V, E23K, K26R, T27A, N64K, T92I, Q102P and H378R. In contrast, carriers of the K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y mutations appear to be protected from infection (Stawiski *et al*., 2020). Recently two other variants (K26R and S331F) have demonstrated reduced binding affinity of the spike protein (S) to the ACE2 (Lanjanian *et al*., 2021). Darbani and colleagues showed that more than half of the ACE 2 susceptibility variants were found in men, which may explain the clinical observations of higher mortality rates in men (Darbani, 2020). Similarly the expression of the ACE2 gene in the nasal epithelium was studied in a cohort of 305 individuals, it was found that children under 10 years of age had the lowest level of ACE2 expression, therefore it was suggested that the benign forms of COVID 19 in children might be due to a lower expression of ACE2 (Bunyavanich *et al*., 2020). Birte Möhlendick and her team appear to be the first to genotypically associate an ACE2 polymorphism, Comparing patients from the "fatal" group (N = 46, 15.5%) to all other SARS-CoV-2-positive patients, they discovered an almost threefold increased fatality risk for ACE2 rs2285666 GG genotype carriers (p=0.002), and alsoa trend for an association with a two-fold increased risk for hospitalization (p = 0.06) in patients with mild course of disease regardless of known risk factors and comorbidities (Möhlendick *et al*., 2021). A recent study by Molina Sabater *et al*., (2022) analyzing ACE2 gene polymorphisms in 318 patients by Sanger sequencing associated heterozygosity of ACE2 SNPs rs2074192 and rs1978124 with a severe clinical course in males at the same time a protective factor in females (p=0.016 and p= 0.038 respectively), while the C/C genotype of rs2106809 and the A allele of rs2285666 in ACE2 are correlated with severity and death in patients with COVID-19 (p= 0.012 and p= 0.0081 respectively) (Sabater Molina *et al*., 2022). In agreement with these results, the ACE2 polymorphisms rs2074192, rs6632677, rs4646142, rs2048683, and rs4240157 were investigated, a significant correlation between COVID 19 severity and the ACE2 SNP rs6632677 (p = 0.027) was determined as a risk factor (J. Wang *et al*., 2022). In the same sense, another recent study from the Iranian Pasteur Institute including 1078 COVID-19 patients

was able to associate the ACE 2 rs2285666 CC genotype with increased mortality rates ($p<0.01$) (Khalilzadeh *et al*., 2022).

Transmembrane serine protease 2 (TMPRSS2):

Variations in the TMPRSS2 gene have also been associated with several viral pathologies and infections. In silico analyses have shown single nucleotide polymorphisms that can affect TMPRSS2 expression and influence the severity of COVID 19. Lalu Muhammad Irham and colleagues studied the gene expression profiles for TMPRSS2 and its important loci in different populations from several large genomic databases and were able to identify 4 SNPs affecting TMPRSS2 protease expression in lung tissue rs464397, rs469390, rs2070788, and rs383510, populations carrying these variants might be relatively susceptible to SARS-CoV-2 infection (Irham *et al*., 2020). Analysis of some of the SNPs cited above by a team of German researchers on a cohort of 492 samples by genotyping rs2070788, rs383510 and rs12329760 in the TMPRSS2 gene were able to associate the rs383510 variant with an increased risk of SARS-CoV-2 infection (Schönfelder *et al*., 2021). Another recent study analyzing 5 SNPs (rs2070788, rs734056, rs12329760, rs2276205, and rs3787950) using next-generation sequencing (NGS) data from 393 patients demonstrated a significant association between the SNP rs2070788 (G allele) and case fatality rate in Indian populations ($p=0.029$), compared with the AG and AA genotypes, rs2070788 Gtended to have significantly higher expression of the TMPRSS2 gene in the lungs (Pandey *et al*., 2022). As for the SNP rs12329760 it has been correlated with severe forms in the European population (Andolfo *et al*., 2021). A meta-analysis carried out in 2022 on the Renin Angiotensin System and gathering 11 studies including 3333 patients with COVID-19 and 5547 controls reports a significant association between the TMPRSS2 rs12329760 C allele and the increased risk of developing a severe form of the infection (Wacharapol *et al*., 2022). A study by Shadat Hossain et al. reports that ACE2, TMPRSS2 and FURIN proteins are functionally related to each other and that several genes are highly co-expressed with them, which could be involved in viral pathogenesis. thus, genetic variants of ACE2, TMPRSS2 and FURIN could alter their normal expression and virus propagation (Hossain *et al*., 2021).

FURIN

FURIN is a protease that plays a key role in SARS-CoV-2 infection. Variants of FURIN have been studied and associated with severe forms of COVID-19 disease in multiple studies. In 2022, it is reported that FURIN rs6224 T ($p= 0.02$) and rs4702A ($p= 0.03$) polymorphisms were significantly increased in ICU deaths (N=106) (Eliecer *et al*., 2022). More recently, a new polymorphism related to severe forms has been reported in the Indian population, it is FURIN rs1981458 detected by NGS sequencing and has been proposed as a severity biomarker to identify vulnerable populations ($p<0.05$) (Pandey *et al*., 2023).

ABO system:

Another avenue of host genetics and SARS-CoV-2 infection involves the ABO system. The Genome Wide-Association (GWAS) study associated blood types with pathogenicity and susceptibility to COVID 19, suggesting that blood type O may be associated with a reduced risk of SARS-CoV-2 infection while blood type A is associated with an increased risk of respiratory failure (The Severe Covid-19 GWAS Group, 2020). However, non-genetic studies have linked this correlation to Anti-A antibodies which could block the interaction of protein S with ACE 2 and have a seroneutralizing effect that provide protection to blood group O (Focosi, 2020). However, this would not explain the severity and critical course of the infection in group A patients. A recent clinical study on a Spanish cohort of 566 patients hospitalized for COVID-19 (236 patients hospitalized in intensive care unit) demonstrated by genotyping that group A genotypes was an important risk factor for developing a severe form of COVID-19 with admission to intensive care ($P= 0.01$) (Gómez *et al*., 2021).

Interferon system:

Numerous clinical studies indicate that the severity of COVID-19 is positively correlated with inflammatory cytokine levels. Indeed, excessive immune responses associated with high levels of proinflammatory cytokine (cytokine storm) after SARS-CoV-2 infection appear to contribute to lung injury and severe acute respiratory distress (pathological course similar to hemophagocytic lymphohistiocytosis) (C. Huang *et al*., 2020). The levels of many cytokines were found to be significantly elevated and showed different expression patterns in patients with different severity of COVID 19 (Yang *et al*., 2020). Hadjaj *et al*., Identified factors suggestive of cytokine storm by studying the expression of 574 immune-related genes in COVID 19 patients of different severities, in critical COVID-19 patients, the type I IFN response was impaired (absence of IFN-β and low IFN-α production and activity), genes involved in type I IFN signaling (such as IFNAR1, JAK1, TYK2) were upregulated, whereas IFN-stimulated genes (ISGs) (such as MX1, IFITM1, IFIT2) were significantly downregulated. In addition, the expression of neutrophil chemokine receptor CXCR2, monocyte chemotactic factor CCL2 and CCR2 receptor were significantly upregulated in severe and critical patients (Hadjadj *et al*., 2020). Pairo castineira et and colleagues also reported reduced IFNAR2 expression and elevated TYK2 expression, identifying TYK2 rs74956615 and IFNAR2 rs2236757 alleles associated with severe forms of the infection (Pairo-Castineira *et al*., 2021). Nhung and his colleagues also exploredCOVID-19 host genetics related to

susceptibility and severity in 200 patients with and 100 controls in Vietnam and were able to associate the TYK2 polymorphism rs 2304255 to sever and fatal outcomes of SARS-CoV-2 infection (p = 0.031), worse outcomes and risk of death were also observed in TYK2 polymorphism rs 2304256 combined to rs1990760/IFIH1 and rs12329760/TMPRSS2 (p= 0.044) (Dieter *et al*., 2022; Nhung *et al*., 2022).

Interferon-induced transmembrane protein 3 (IFITM3) is another widely studied lead as it acts as a regulator of antiviral immunity, controls cytokine production and affects the severity of infections against viruses (Nikoloudis *et al*., 2020). A team of researchers performed genotyping tests on 880 Saudi patients and were able to demonstrate that the SNP rs12252 of IFITM3 is associated with severity, hospital admission (p=0.04) and mortality (p=0.01) following SARS-CoV-2 infection in Saudis under 60 years of age, on the other hand the plasma levels of IFNγ in this cohort were significantly lower in patients with AG/GG genotypes than in patients with AA genotype (p=0.00016) (Alghamdi *et al*., 2021). Moreover, a meta-analysis by Yapeng li and his team including 1989 patients was able to associate IFITM3 rs12252 with susceptibility to COVID-19 and rs12252-C with severe forms (Li *et al*., 2022).

The IFNAR2 protein is a type I interferon receptor that plays an important role in the regulation of the immune response and it has been implicated in the severity of COVID-19. Indeed, in 414 patients with COVID-19 admitted to intensive care unit, the IFNAR2 rs2236757 A/A genotype was associated with the risk of ICU admission (p=0.045) (Dieter *et al*., 2022). In the same sense, another study by Mohammad Abdelhafez and his team evokes the rs2236757A polymorphism being associated with critical forms of infection in Palestinian patients (p< 0.025) (Abdelhafez *et al*., 2022).

Apolipoproteine E:

Authors report that there is a correlation between apolipoproteine E (ApoE) and the severity of COVID 19 since the latter could facilitate the entry of the SARS-CoV-2 virus and modify intracellular cholesterol levels (H. Wang *et al*., 2020). Javad Safdari lord *et al*., (2022) recently studied the association of Apolipoprotein E, ApoE genotype with severe forms of COVID 19 in 201 patients and were able to demonstrate that the e4 allele and the e4/e4 genotype increased the risk of severity of infection 5 to 17 times respectively and that ApoE is independently associated with severe forms (p= 0.0001), This is in agreement with the results previously published by Kuo et al. who also linked the presence of the APOE e4/e4 allele to the severity of COVID 19 regardless co-morbidities (p= $2.42x10^{-7}$) (Kuo *et al*., 2020).

Dipeptidyl peptidase:

In the literature, the expression levels of different dipeptidyl peptidase enzymes and their associations with severe forms of the disease have been reported in several studies. More recently, we find the study of Rosalinda Posadas-Sánchez and her team who observed low levels of DPP4 in patients with severe forms of COVID-19 (p= $1.69x10^{-11}$), as well as rs3788979 DPP4 polymorphism associated with a high risk of infection (p=0.001), and patients rs3788979 TT genotype carriers had the lowest dpp4 levels (Posadas-Sánchez *et al*., 2021). In addition, Dipeptidyl peptidase 9 (Dpp9) is a crucial immunomodulatory factor in T cell proliferation and pro-inflammatory cytokine production, and its expression level in severe COVID 19 patients is significantly increased compared to healthy subjects (Sharif-zak *et al*., 2022). A genetic analysis conducted in Vietnam by whole exome sequencing associated the SNP rs2277735 (AG genotype) of DPP9 were associated with the severity and mortality of COVID-19 (p=0.01) (Nhung *et al*., 2022).

Leucine Zipper Transcription Factor-Like Protein 1 (LZTFL1):

In addition to TYK2, DPP9, IFNAR2, CCR2 and ABO genes, GWAS indicated that the 3p21.31 loci including Leucine Zipper Transcription Factor-Like Protein 1 (LZTFL1) and chemokine receptor genes, is strongly associated with severe cases of COVID-19 (Ferreira *et al*., 2022). This could explain the complications and high mortality rate in COVID-19 patients with cancer, taking into consideration the oncogenic roles of LZTFL1 and its expression in different tumor types (Al-Quteimat & Amer, 2020; Jihao *et al*., 2022). Furthermore, LZTFL1 has been identified as a marker for a twofold higher risk of severe forms of COVID-19 (Downes *et al*., 2021). Researchers in Bogota, Colombia, were able to identify by Sanger sequencing the LZTFL1 rs11385942 polymorphism as a risk factor for hospitalization and suggest this polymorphism as a biomarker for the severity of COVID-19 (p<0.01) (Angulo-Aguado *et al*., 2022). In the same sense, Iris M.Fink-Baldauf and her team performed a CRISPRi gene expression analysis and also identified LZTFL1 rs11385942 as a risk allele in patients infected with SARS-CoV-2 (p < 0.05) (Fink-Baldauf *et al*., 2022). Same result obtained in Najaf province, population genome analysis associates rs11385942 with the severity of Covid-19 (p < 0.001) (Razaq & Alkufi, 2022). The SNP rs17713054 of the LZTFL1 gene was analyzed by RFLP PCR in a study conducted by Russian researchers and were able to correlate this SNP with the high risk of epithelial dysfunction with evidence of epithelial-mesenchymal transition in COVID-19 (Pavlova *et al*., 2022).

Human Leukocyte Antigen (HLA):

The HLA (Human leukocyte antigen) system plays an important role in the immune response to several viral infections, including SARS-CoV-2. Indeed, studies have demonstrated the association of certain HLA haplotypes with the severity of COVID-19 (Ansari *et al*., 2022). However, it is important to note that these results are not uniform in all populations studied. A July 2022 Meta-analysis including 19 studies with 10,551 SARS-CoV-2 positive patients reported an association with COVID-19 severity or lethal outcome of alleles at the HLA-A, -B, -C, -DRB1, -DQB1 (Zorana *et al*., 2022). Another meta-analysis by Paroma Deb and his team including 36 articles and 794,571 participants reported that although several HLAs described a significant association, the heterogeneity of HLA typing methods and study designs as well as conflicting results do not allow a conclusion on the role of HLAs in the severity and mortality of COVID-19 (Paroma *et al*., 2022). The team of Juan Francisco Gutiérrez-Bautista recently studied the previously cited polymorphisms of HLA class I (HLA-A, -B and -C) as well as HLA class II (HLA-DRB1 and HLA-DQB1) in 450 patients, and could not demonstrate any relationship between HLA polymorphisms or haplotype to disease severity (Gutiérrez-Bautista *et al*., 2022). Further research is needed to identify an underlying genetic correlation of the HLA system to the severity of COVID 19.

Killer cell Immunoglobulin-like Receptor (KIR):

Activation of natural killer NK cells is regulated by killer cell immunoglobulin-like receptors (KIRs), their genes are located on chromosome 19q13.4. The KIRs and their ligands, the MHC class 1 molecules (HLA-A B and C) are highly polymorphic (Dizaji Asl *et al*., 2021). Some studies confirm the crucial role of NKs and KIR/ligand interactions in the clinical variability of COVID 19 (Bernal *et al*., 2021). Using next-generation sequencing (NGS) in 424 patients, Ali Hajeer and his team were able to confirm the association of KIR2DS4 and KIR3DL1, which are part of the KIR A inhibitory haplotype, at risk for severe SARS-CoV-2 infection (p=0.0007) (Hajeer *et al*., 2022).

CONCLUSION

The emergence of the COVID-19 pandemic has led to a significant amount of research into the genetic factors that may impact host susceptibility and severity to the infectious diseases. In this review, we provide several studies that have identified various genes and relevant genetic polymorphisms that are associated with an increased risk of developing severe form of COVID-19. Most of these genetic variants can be used as a genetic biomarker to predict the severity of SARS-CoV-2 infection. This paper is the first review carried out in Morocco. Further research and studies are needed to fully understand the genetic underpinnings of COVID-19 in several countries for further data sharing.

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