Review

Effects of host genetic variations on response to, susceptibility and severity of respiratory infections

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1. Introduction

The recent pandemic of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) and created a global crisis, devastating health organizations and perplexing researchers to find the solution for this problem. Meanwhile, it has raised the question whether genetic factors can define the susceptibility to the disorder or the severity of symptoms. Although few studies have tried to answer the question [1], it seems to be too early to reach a conclusive result in this regard. Yet, previous studies have indicated that susceptibility to respiratory tract infections is determined by both genetic and acquired risk factors [2]. As SARS-CoV-2 exploits angiotensin converting enzyme 2 (ACE2) for its entrance inside the cells, this gene is a putative risk factor for this infection [3,4]. Being located in a genomic region on chromosome X that escapes from X inactivation, it has a heterogeneous sex bias expression in different tissues [5]. Higher levels of its expression in male tissues have been attributed to 17β-estradiol-dependent and sex chromosome-independent mechanisms [6]. Fig. 1 shows the role of some polymorphisms is ACE2 and other genes in the course of SARS-CoV-2 infection.

2. SARS-CoV

Itoyama et al. have investigated the role of ACE1 insertion/deletion (I/D) polymorphism in conferring risk of SARS or disease course in the Vietnamese individuals. They reported higher frequency of the D allele in the hypoxemic group compared with the non-hypoxemic group. However, there was no remarkable difference in the frequency of these alleles between the SARS-CoV cases and non-affected individuals.
infection was correlated with HLA-B*4601 [14]. The severity of SARS-CoV infection, when comparing infected SARS patients bearing pseudotype associated infection in permissive cells, Chan et al. reported effects for severe SARS-CoV infection [12]. Based on the previously reported effects of CD209 in the promotion of SARS-CoV spike protein-bearing pseudotype associated infection in permissive cells, Chan et al. have assessed association between a variant within this gene and clinical outcome of patients with SARS-CoV infection. SARS patients who were formerly genotyped for FcγRIIA SNPs. They found a heterogeneous sex bias expression in different tissues [5]. The AA genotype of the rs2285666 is associated with higher expression of ACE2. Based on the role of ACE2 as the cell receptor for entrance of the virus, the mentioned polymorphism might affect the infection course [1]. The rs1024611 is located in the transcript start site of the CCL2 gene and might affect expression of the corresponding gene. The GG genotype of this polymorphism is associated with higher levels of CCL2. CCL2 is a chemokine that regulates chemotaxis and secretion of inflammatory mediators from monocytes and macrophages [7]. The rs2070874 polymorphism is located in the 5' UTR of IL-4 gene and might influence transcription of this gene [8]. IL-4 down-regulates ACE2 receptor, thus preclude SARS-CoV entrance into the cells [9].

ACE2 gene is located on chromosome X, in a genomic region which escapes from X inactivation. Yet, it has a heterogeneous sex bias expression in different tissues [3]. Cao et al. have assessed the functional role of 1700 ACE2 single nucleotide polymorphism (SNP) array in a large cohort of Italian individuals as an illustrative model of the whole population. Then, they compared the presence of rare variants and the occurrence of SNPs with Europeans and East Asians. Besides, they searched the gene expression catalogues to examine the sex-biased expression. Surprisingly, they detected no remarkable clue for association between ACE2 and COVID-19 severity/sex bias in the Italian population. Yet, expression levels and SNPs of TMPRSS2 were identified as putative modulators of this disorder explaining the reported statistics among Italian patients. Yet, the obtained results should be verified through experimental analyses in large sample sizes of affected individuals with various clinical presentations [1]. Renieri et al. have retrieved the exome data of 7000 individuals from the Network of Italian Genomes to assess the ACE2 variants. They recognized some variants with a potential effect on the stability of the ACE2 protein. Three missense variants with minor allele frequencies between 0.002 and 0.015 were anticipated to alter protein cleavage and stabilization. The variants p.Asn720Asp, p.Lys26Arg, p.Gly211Arg have not been detected in the Eastern Asia population. Besides, Lin et al. have assessed association between HLA alleles and SARS-CoV infection in Asian population. HLA-B*4601 and HLA-B*5401 were reported as the most probable factors in confirming risk of infection, when comparing infected SARS patients and high risk health care workers individuals. The severity of SARS-CoV infection was correlated with HLA-B*4601 [14].

Asselta et al. have recently investigated the putative genetic elements of the strange severity of COVID-19 among Italians. They have observed the transcript levels and genetic polymorphisms in ACE2 and TMPRSS2 genes, which have been shown to be involved in the process of viral infection. They have assessed the data of exome and single nucleotide polymorphism (SNP) array in a large cohort of Italian individuals as an illustrative model of the whole population. Then, they compared the presence of rare variants and the occurrence of SNPs with Europeans and East Asians. Besides, they searched the gene expression catalogues to examine the sex-biased expression. Surprisingly, they detected no remarkable clue for association between ACE2 and COVID-19 severity/sex bias in the Italian population. Yet, expression levels and SNPs of TMPRSS2 were identified as putative modulators of this disorder explaining the reported statistics among Italian patients. Yet, the obtained results should be verified through experimental analyses in large sample sizes of affected individuals with various clinical presentations [1]. Renieri et al. have retrieved the exome data of 7000 individuals from the Network of Italian Genomes to assess the ACE2 variants. They recognized some variants with a potential effect on the stability of the ACE2 protein. Three missense variants with minor allele frequencies between 0.002 and 0.015 were anticipated to alter protein cleavage and stabilization. The variants p.Asn720Asp, p.Lys26Arg, p.Gly211Arg have not been detected in the Eastern Asia population. Besides, Lin et al. have assessed association between HLA alleles and SARS-CoV infection in Asian population. HLA-B*4601 and HLA-B*5401 were reported as the most probable factors in confirming risk of infection, when comparing infected SARS patients and high risk health care workers individuals. The severity of SARS-CoV infection was correlated with HLA-B*4601 [14].
### Table 1

| Gene | Disease | SNP | Sample | Population | Comment |
|------|---------|-----|--------|------------|---------|
| TMPRSS2 | SARS-CoV-2 | rs463727, rs34624090, rs55964536, rs734056, rs4290734, rs34783969, rs11702475, rs35899679, rs35041537, rs2070788, rs9974589, rs7364083 | General: 125,748 WES, 71,702 WGS, Italian: 3,984 WES | Two haplotypes were supposed to increase TMPRSS2 expression in an androgen-specific way. PA6/70264p and pA6/70211 were predicted to interfere with the A6-840p protein, thus desaturating the proprotein structure. The A6 allele was associated with disease susceptibility and mortality. | [1] |
| ACE2 | SARS-CoV-2 | rs2285666 | General: 125,748 WES, 71,702 WGS, Italian: 3,984 WES, 3,284 GWAS | Three populations with heterogeneous ARDS risk factors. The A allele is more frequent in Italian and the AA genotype confers ACE2 higher expression level. | [1] |
| ACE | SARS-CoV-2 | rs11217134, rs12010448, rs143695310, rs1996225, rs200781818, rs2158082, rs4060, rs4646127, rs4830974, rs4830983, rs5936011, rs5936029, rs6629110, rs6632704, rs75979613 | 3,284 GWAS | 46 cases Hypoxemic/non-hypoxemic | [10] |
| IL1RN | ARDS | rs315952 | Three populations with heterogeneous ARDS risk factors. | 300/300 Chinese | C allele was associated with decreased risk. | [21] |
| IL-10 | ARDS | rs1800872, 819C > T | 51 cases at the time of ECMO installation/ 6 hours later | 519 cases/11 dead | Taiwanese | [22] |
| IL-6 | ARDS | rs1800796 | Three populations with heterogeneous ARDS risk factors. | 300/300 Chinese | G allele was associated with ARDS risk. | [7] |
| TNF-α | ARDS | rs1800629 | Three populations with heterogeneous ARDS risk factors. | 300/300 Chinese | The A allele was a risk factor for ARDS, GG genotype was significantly associated with lower mortality. | [25] |
| CCL2 | SARS-CoV-2 | rs1024611 | 932/982 Chinese | 46 cases Hypoxemic/non-hypoxemic | GG genotype was associated with the increased risk of SARS. | [7] |
| CCL5 | Bronchiolitis | rs2107538, rs2280788 | 181 infants/536 healthy adults Brazilian | 300/300 Chinese | G allele was associated with bronchiolitis caused by respiratory syncytial virus (RSV). | [19] |
| TNF | Sepsis | rs1800629, -863 C > A | 490 septic pediatric patients | 300/300 Chinese | -308 GA was associated with susceptibility to SARS. | [28] |
| IFN-γ | SARS +874 A > T | 495/578 Chinese | +874A allele was associated with susceptibility to SARS infection. | 420/316 Chinese | C allele was associated with higher risk of Apache. | [11] |
| IFN-γ | Pulmonary tuberculosis +874 A > T | 495/578 Chinese | +874A allele was associated with susceptibility to SARS. | 585 Chinese | +874A allele was associated with susceptibility to SARS. | [11] |
| TLR1 | Sepsis | rs5743551 | 711/775 | Caucasian | -7292 G was associated with increased risk of SIRS, higher mortality, increased susceptibility to organ dysfunction, death, and gram-positive infection. | [11] |
| TLR2 | Tuberculosis | rs1898530, rs7664411 | 352/324 Brazilian | 300/300 Chinese | A allele was associated with increased risk of SIRS, higher mortality, increased susceptibility to organ dysfunction, death, and gram-positive infection. | [11] |
| TLR4 | RSV, Bronchiolitis | rs4986790, rs1927911 | 181 infants/536 healthy adults Brazilian | 312/356 Brazilian | A allele was associated with increased risk of SIRS, higher mortality, increased susceptibility to organ dysfunction, death, and gram-positive infection. | [11] |
| TLR10 | Tuberculosis | rs1758983, rs11536889 | 420/316 Chinese | 490 septic pediatric patients | -308 GA was associated with susceptibility to SIRS. | [28] |
| (continued on next page) | | | | | | |
variants. They reported no indication of the presence of coronavirus S-protein binding-resistant ACE2 mutants in various ethnic groups. The East Asian populations were shown to have higher allele frequencies in the eQTL variants correlated with elevated expression of ACE2 in tissues. Thus, they conclude the role of these variants in the inter-population variability in the risk of SARSCoV-2 infection or host response to this virus [15].

### 4. Influenza

Cheng et al. have assessed the role of possible genetic factors that influence the risk of severe H1N1 and H7N9 Influenza infections. They conducted a pilot genome-wide association study (GWAS) and a subsequent assessment of the expression quantitative trait locus (eQTL) data set in the lung tissue. They recognized the GG genotype of rs2070788 as a risk factor for severe H1N1 infection. This variant has been associated with elevated expression of TMPRSS2. They also identified a putative functional SNP namely rs383510 which tags with rs2070788. Functional studies confirmed the regulatory role of rs383510 on TMPRSS2 expression in a genotype-specific mode. Both SNPs were associated with the risk of H7N9 Influenza. Taken together, SNPs that increase TMPRSS2 expression are regarded as risk variants for severe H1N1 influenza. Moreover, these variants confer risk of H7N9 influenza [16]. Zhou et al. have shown association between the rs2564978 genotype T/T of CD55 and severe H1N1 infection. They also reported an allele-specific impact on CD55 expression which was attributed to a promoter indel variation located in the complete linkage disequilibrium with rs2564978. CD55 can guard epithelial cells of the respiratory system from complement harm. Moreover, the H1N1 infection enhanced CD55 expression [17]. Moreover, To et al. have reported an association between the C allele of rs1130866 in the surfactant protein B gene (SFTPB) and severe H1N1 disease [18].

### 5. Respiratory syncytial virus (RSV)

Alvarez et al. reported association between SNP rs2107538 of CCL5 and bronchiolitis caused by RSV. In addition, the rs4986790 ofTLR4, rs1898830 ofTLR2, and rs2228570 ofVDR were regarded as risk factors for progression to death [19]. Löfgren et al. have shown association between the Gly299Gly genotype ofTLR4 and protection against severe RSV during the year 2000 epidemics. Yet, they did not verify the association between the Gly299Gly genotype of TLR4 and protection against severe RSV [20].

### 6. Acute respiratory distress syndrome (ARDS)

Meyer et al. have reported association between the IL1RN SNP rs315952 C allele and lower risk of ARDS in three distinct group of patients with different ARDS risk factors. Notably, this variant was associated higher plasma IL1RA response. IL1RA has been shown to reduce ARDS risk [21]. Liu et al. have shown association between elevated interleukin (IL)-10 levels and two SNPs (-592 C and -819 C) at the promoter region of the corresponding gene. Notably, in patients with ARDS, there was a significant association between IL-10 levels at the time of installation of extracorporeal membrane oxygenation and poor prognosis [22]. Gong et al. also verify the association between the −1082G genotype of IL-10 and development of ARDS. Yet, this genotype had a significant interaction with age. Among patients with ARDS, this genotype was associated with reduced severity of disorder on admission as well as deceased mortality and organ damage. Thus, the high IL-10-producing −1082G genotype may be related to different risk values of ARDS depending on age [23]. However, in a population of patients with community acquired pneumonia, the −1082 G allele was associated with higher expression of IL-10 and increasing severity of the condition [24]. Ding et al. have demonstrated

| Gene | Disease | SNP | Sample | Population | Comment |
|------|---------|-----|--------|------------|---------|
| TLR9 | Bronchiolitis | rs352162, rs187084 | 181 infants/536 healthy adults Brazilian | Associated with disease severity [19] |
| CD14 | Sepsis | rs2563298 | 152/199 Chinese | C allele was associated with susceptibility to sepsis. [18] |
| −159C > T | rs2569190 | 152/198 Chinese | 159 CC is associated with severe SARS infection. [12] |
| CD55 | Influenza | | | |
| CD209 | SARS | | | |
| SFTPB | Influenza | −1580C > T | 402 Cases African American, Asian, White, South African, Asian, | −1580 C is associated with ARDS, septic shock, and CAP severity. [15] |
| VDR | Bronchiolitis | rs2228570 | 181 infants/536 healthy adults Brazilian | Associated with disease severity [19] |
| RSV | | rs10735810 | 296/113 South African | T allele was associated with the disease susceptibility. [32] |
| HLA | Influenza | | | Association of HLA alleles with the susceptibility of disease. [33] |
| −A*11, HLA−B*35, HLA−DRB1*10, HLA−DRB1*15 | 33 patients/101 HCW/190 | | | Association of HLA alleles with the susceptibility of disease. [33] |
| −H1082G, HLA−B*4601, HLA−B*5401 | 33 patients/101 HCW/190 | | | Association of HLA alleles with the susceptibility of disease. [33] |

### Acute respiratory distress syndrome (ARDS), expression quantitative trait locus (eQTL), Whole Exome Sequencing (WES), Extracorporeal membrane oxygenation (ECMO), Community acquired pneumonia (CAP), SARS-Coronavirus and pneumonia, The respiratory syncytial virus (RSV), Inflammatory response syndrome (SIRS), Health care workers (HCW), Pneumococcal disease: tuberculosis, influenza, respiratory syncytial virus, SARS-Coronavirus and pneumonia. The respiratory syncytial virus (RSV), lactate-dehydrogenase (LDH).
associations between the TNF-α rs1800629 A allele and the IL-6 rs1800796 G allele and higher susceptibility to ARDS. Moreover, they reported a protective role for the G allele at MyD88 rs7744 against ARDS. These SNPs have been shown to influence the survival rate of patients as well [25].

Table 1 summarizes the results of studies which appraised the role of SNPs in susceptibility to respiratory disorders or the severity of these conditions.

### 7. Discussion

With the progression of the COVID-19 pandemic, the need for identification of prognostic biomarkers for susceptibility to severe disease is emerging. The current data about the role of genetic risk factors in the determination of rate of SARS-CoV-2 infection in each ethnic group and the severity of disorder is limited and is not validated by experimental assays. Moreover, several confounding parameters such as the number of tests performed in each country, the structure of the population especially the age distribution, the presence of risk factors for respiratory disorders such as smoking and other environmental factors might be involved in the variability in disease course or prevalence of infection among different ethnic groups [1]. Yet, assessment of the obtained data of association between genetic variants and other relevant viruses such as SARS-CoV might be helpful in this regard. Notably, several genetic loci have been shown to influence the risk of ARDS, a condition which is associated with severe COVID-19 infection. Thus, these genetic variants might also modulate the progression of COVID-19 in the affected patients. These SNPs mostly affect the levels of pro-inflammatory and anti-inflammatory cytokines. However, the results of these studies should be verified in different ethnic groups. Moreover, a number of variants have been associated with more than one of the mentioned disorders. For instance, the rs2070788 of TMIPRSS2 is associated with SARS-CoV2 as well as influenza. Similarly, rs1800629 of TNFα is associated with ARDS as well as sepsis. Besides, rs1800896 is associated with higher levels of IL-10, ARDS, severity of community acquired pneumonia (CAP) and septic shock from Pneumococcal diseases. The rs2430561 of IFNγ is associated with pulmonary tuberculosis and SARS. Finally, the rs1130866 of SFTPβ has been associated with severity of CAP and influenza. These data indicate the role of these variants in defining the host response to these infections which is probably exerted through modulation of immune responses.

There is a necessity for conduction of inclusive investigations that integrate genomic information, epidemiological statistics, and medical records of the clinical manifestation of patients with COVID-19. The final conclusive results are expected to obtain from application of a systems biology approach to assess the data of high throughput sequencing methods. These results permit conduction of an evidence-based risk assessment and the subsequent implementation of preventive and therapeutic modalities in a personalized manner.

### Declaration of Competing Interest

The authors declare they have no conflict of interest.

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