Review

Host genetic factors determining COVID-19 susceptibility and severity

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ABSTRACT

The COVID-19 pandemic caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) poses an unprecedented challenge to humanity. SARS-CoV-2 infections range from asymptomatic to severe courses of COVID-19 with acute respiratory distress syndrome (ARDS), multiorgan involvement and death. Risk factors for disease severity include older age, male sex, increased BMI and pre-existing comorbidities. Ethnicity is also relevant to COVID-19 susceptibility and severity. Host genetic predisposition to COVID-19 is now increasingly recognized and whole genome and candidate gene association studies regarding COVID-19 susceptibility have been performed. Several common and rare variants in genes related to inflammation or immune responses have been identified. We summarize research on COVID-19 host genetics and compile genetic variants associated with susceptibility to COVID-19 and disease severity. We discuss candidate genes that should be investigated further to understand such associations and provide insights relevant to pathogenesis, risk classification, therapy response, precision medicine, and drug repurposing.

1. Introduction

2019 coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected millions of people worldwide. SARS-CoV-2 belongs to the *Coronaviridae* family, which includes the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-1), the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and four seasonal coronaviruses that cause mild infections [1,2].

The clinical spectrum of COVID-19 ranges from asymptomatic, mild to moderate, severe, and critical disease. The most common symptoms are fever, cough, headache, fatigue, breathing difficulties, anosmia and ageusia. Approximately one-third of those infected are asymptomatic. Among symptomatic patients, 81% have mild to moderate symptoms, 14% develop severe symptoms (dyspnea, hypoxia, lung involvement on imaging); 5% experience respiratory failure, ARDS, shock, or multiorgan failure) [3]. Worldwide, the case fatality rate is between 1 and 10% and 17% in hospitalized patients, with disparities related to variable sizes of the denominator, the number of individuals tested, demographics,

ethnicity, functionality of health care systems and virus variants [4]. Undetected cases during the first wave have caused considerable underestimation of asymptomatic infections [5].

A common feature in critical illness is immune dysregulation and a cytokine storm (CS) [6,7] with a sudden increase in proinflammatory cytokines and other inflammatory markers. This hyperinflammatory syndrome causes coagulopathies, oxidative stress, organ damage, and death [7], in line with COVID-19 being primarily a vascular, rather than a pure respiratory disease [8]. Rarely, children experience a multisystem inflammatory syndrome (MIS-C). A MIS may also occur in adults (MIS-A) [9].

Risk factors are older age, male sex, and comorbidities including chronic lung disease, cardiovascular disease and hypertension, diabetes, obesity and cancer [10–12], but also ethnicity [13,14]. Additionally, host genetic factors were proposed as risk factors of SARS-CoV-2 infection or severe courses of COVID-19.

To identify host genetic factors associated with the course of SARS-CoV-2 infections, genome-wide association studies (GWAS), whole-exome sequencing (WES), and candidate gene studies have been performed by several consortia (COVID-19 Host Genetics Initiative [HGI] [15], Genetics Of Mortality In Critical Care [GenOMICC] [16], COVID human genetic effort [17], independent academic working groups, and commercial genomics service providers such as

23andMe [18] and AncestryDNA [19]. Several single nucleotide polymorphisms (SNPs) and genes associated with infection susceptibility or distinct aspects of disease severity, such as hospitalization requirement, respiratory failure, or death were identified. Many genes highlighted in genetic studies on COVID-19 are implicated in key pathophysiological processes, including viral entry into cells, immunity, and inflammatory responses. Notably, association studies of COVID-19 were mostly conducted in Caucasian populations, while previous SARS association studies were mainly conducted in East Asian populations. African, South Asian, and South American ethnicities remain largely underrepresented in COVID-19 host genetic research.

2. GWAS variants associated with COVID-19

Multiple GWASs have investigated host genetic variants in clinical phenotypes of COVID-19 severity/susceptibility [16,18−20]. HGI [15] updates its GWAS metanalysis (most recent release HGI 6 (https://www.covid19hg.org/results/r6/). GWASs have identified various loci associated with infection susceptibility or COVID-19 severity, which were characterized further by colocalization analyses or Mendelian randomization (MR). We discuss currently relevant GWAS loci (Table 1, Fig. 1) and their implications for disease pathogenesis and treatment options.

2.1. 3p21.31

The first GWAS identified the 3p21.31 locus (rs11385942) associated with severe COVID-19 and respiratory failure [20]. 3p21.31 lies in a gene cluster containing the genes sodium-imino acid transporter 1 (SIT1) (*SLC6A20*), human leucine zipper transcription factor like 1 (*LZTFL1*), CC motif chemokine receptor 9 (*CCR9*), FYVE and coiled-coil domain-containing protein 1 (*FYCO1*), C-X motif chemokine receptor 6 (*CXCR6*), and X-C motif chemokine receptor 1 (*XCR1*) genes [20]. This signal was replicated by GWAS [16] and commercial genetic testing. 23andMe confirmed that the locus is associated with respiratory symptoms [18] while Roberts et al. from AncestryDNA, whose study is published as a preprint, found only a nominal association with hospitalization [19]. The 3p21.31 locus was also significant in the HGI metanalysis, which identified two signals within the locus, one associated with severity (rs10490770), the other with infection susceptibility (lead variant rs2271616) [15].

Although causal variants of 3p21.31 signals have not been firmly established, evidence points to SLC6A20, a sodium transporter interacting with ACE2, the SARS-CoV-2 cell surface receptor [21]. *SLC6A20* was proposed as causal gene for the susceptibility signal discovered by the HGI (lead variant rs2271616) [15]. 3p21.31 also harbours the chemokine receptor genes *CCR9, CXCR6* and *XCR1. CXCR6* recruits CD8-resident memory *T*-cells in the respiratory tract to combat respiratory pathogens [22]. Evidence for *CXCR6* comes from pQTLs in the 3p21.31 region [23] and transcriptome-wide association studies (TWAS), showing reduced *CXCR6* expression in lungs of severely affected patients [24]. Concordantly, HGI prioritizes *CXCR6* as the likely causal gene at the severity signal (lead variant rs10490770) [15]. The second chemokine receptor at 3p21.31. CCR9, is expressed on *T*-cells and serves as receptor for the chemoattractant thymus-attracted chemokine (TECK, also CCL25) [25]. It is a key regulator in early respiratory allergic inflammation. *SLC6A20* and *CCR9* have been suggested as causative genes at this locus in CRISPR/Cas9 genome editing in myeloid, lymphoid, and erythroid cells [26].

SLC6A20 is the most promising candidate to explain increased susceptibility, while a reduction in CXCR6 might explain a higher risk for severe disease. As no other locus has such strong evidence, its mechanism of action should urgently be targeted in future studies.

2.2. ABO locus

The second locus at 9q34.2 [20] overlaps with the *ABO* locus. Protective effects of blood group *O* were seen, while blood group *A* was associated with severe COVID-19 [20]. The association was replicated [18,19]. HGI found that the *ABO* locus was rather a susceptibility than a severity locus, as it associated with reported SARS-CoV-2 infections and, less significantly, with hospitalization, but not with critical illness [15]. It is also conceivable that this association can be attributed to protection exerted by anti-*A* IgG antibodies and not the blood group antigens [27]. Moreover, blood group *O* was associated with lower ACE1 activity, which might reduce the risk of hypertension and cardiovascular disease, both indicators for severe COVID-19 [28].

To investigate the role of *ABO* in COVID-19, it was investigated whether SNPs identified in 4418 GWASs of other disease traits were in linkage disequilibrium (LD) with observed earlier associations [29]. In previous GWASs, *ABO* associations with plasma levels of eight proteins had been reported, including factor VIII and von Willebrandt factor, IL-6, TNF-alpha, CD209 (DC-SIGN), Tie-1, mannose-binding protein C and fibroblast growth factor 23 [29]. The *ABO* association with coagulation factors suggests an influence on COVID-19 via enhanced coagulation, as reported in COVID-19 patients with CS [30]. In further analyses, the authors focused on CD209, member of the *C*-type lectin family and alternative entry receptor for SARS-CoV-2 [31]. By means of colocalization analyses, a likely causal variant for increased CD209 expression, rs505922, was identified [29]. This trans-eQTL (expression quantitative trait locus) of CD209 was replicated in two MR studies employing HGI data. The variant was found associated with increased CD209 levels and COVID-19 severity [32,33]. Another study interpreted rs505922 as a cis-eQTL of the ABO protein, raising the question as to whether it was decreased ABO plasma protein levels rather than blood group O that exerting protection [34].

Facilitated viral entry due to high CD209 expression aligns with *ABO* being a susceptibility locus described by HGI. The CD209 promotor polymorphism rs4804803 was implicated as risk SARS severity variant in candidate gene studies [35]. Interestingly, CD209 is also an alternative SARS-CoV-1 receptor [31]. rs4804803 affects expression of CD209 *in vitro* and is also associated with susceptibility to HIV-1, *Mycobacterium tuberculosis* and HTLV-1 infections [36−38].

2.3. Interferon-alpha and -beta receptor subunit 2 (IFNAR2)

Pathogen recognition receptors of the innate immune system, e.g., toll-like receptors (TLRs), recognize pathogen-associated molecular patterns and activate interferon-related immune responses. They stimulate production of proinflammatory cytokines via NF-kB activation and activate the interferon regulatory factors (IRFs), which induce type 1 interferon (IFN) expression [39]. IFNAR2 binds type 1 IFNs and is involved in signal transduction by activating the JAK-STAT pathway [40]. This leads to expression of interferon-stimulated genes (ISGs) and triggers early host responses to viral infections. The *INFAR2* variant rs2236757 was found associated with critical COVID-19 [16]. This association was replicated by the HGI, who showed an association of *IFNAR2* rs13050728 with critical illness and hospitalization [15]. Increased expression of IFNAR2 reduced the risk of critical illness, consistent with IFN1 pathways in antiviral defense [16]. These findings were replicated in two further MR studies, with high IFNAR2 expression potentially conferring protection [34,41].

Efficient IFN1-mediated antiviral responses are critical for viral clearance. SARS-CoV-2 antagonizes induction of type 1 IFNs [6] and SARS-CoV-2 inhibits IFN responses through structural proteins. Decreased plasmacytoid dendritic cell counts (pDCs), observed in severe COVID-19, may be responsible for deficient IFN-I responses, as pDCs are prominent producers of IFN-I upon viral infection [6]. Concordantly, SARS-CoV-2 was shown to infect human lung explants

Table 1
Genome wide association studies (GWAS) on COVID-19.

Function	Gene/Locus	Variant	Population	Study design	Sample size	Outcomes	Refs.
Multiple	*SLC6A20, LZTFL1,CCR9, FYCO1, CXCR6 and XCR1*	rs11385942	Spanish and Italian	COVID-19 respiratory failure vs. controls	Italy: 835 patients and 1255 controls, Spain: 775 patients and 950 controls	Associated with respiratory failure	[20]
Multiple	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1*	rs73064425	British	COVID-19 critical illness vs. matched controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Multiple	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1*	rs13078854	All populations (80% European)	COVID-19 positives vs. negatives	15,434 positives vs.121,121 negatives and 1131 hospitalized vs. 1035,598 controls	Associated with severity	[18]
Multiple	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1*	rs17713054	European	COVID-19 positives vs. negatives	2417 positives. vs. 14,933 negatives and 250 hospitalized vs. 1967 not hospitalized	Associated with hospitalization	[19]
Multiple	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1*	rs2271616	Multiple	COVID-19 infection vs. population	112,612 cases vs. 2,474,079 controls	Associated with susceptibility	https://www.covid19hg.org/results/r6/
Multiple	*SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1*	rs10490770	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with hospitalization	https://www.covid19hg.org/results/r6/
Multiple	*ABO*	rs657152	Spanish and Italian	COVID-19 respiratory failure vs. controls	Italy: 835 patients and 1255 controls, Spain: 775 patients and 950 controls	Blood group A associated with respiratory failure	[20]
Multiple	*ABO*	rs9411378	All populations (80% European)	COVID-19 positives vs. negatives	15,434 positives vs.121,121 negatives and 1131 hospitalized vs. 1035,598 controls	Blood group A associated with COVID-19 positivity	[18]
Multiple	*ABO*	rs657152	European	COVID-19 positives vs. negatives	2417 positives. vs. 14,933 negatives and 250 hospitalized vs. 1967 not hospitalized	Nominally associated with hospitalization	[19]
Multiple	*ABO*	rs657152	British	Critical illness vs. controls	2244 critically ill patients and controls	No association with critical illness	[16]
Multiple	*ABO*	rs912805253	Multiple	COVID-19 infection vs. population	112,612 cases vs. 2,474,079 controls	Associated with susceptibility	https://www.covid19hg.org/results/r6/
Innate	*IFNAR2*	rs2236757	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Multiple	*IFNAR2*	rs13050728	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/
Innate	*OAS3; OAS1*	rs10735079; rs4766664	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Innate	*OAS1*	rs10774671	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/
Antiviral	*DPP9*	rs2109069	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Antiviral	*DPP9*	rs2109069	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/
Cytokines	*ICAM5/TYK2*	rs1108572; rs74956615	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Cytokines	*TYK2*	rs74956615	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/
Innate and adaptive	*HLA-G*	rs9380142	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Innate and adaptive	*CCHCR1*	rs143334143	British	Critical illness vs. controls	2244 critically ill patients and controls	Associated with critical illness	[16]
Multiple	*HLA-DPB1*	rs2071351	Multiple	COVID-19 infection vs. population	112,612 cases vs. 2,474,079 controls	Associated with susceptibility	https://www.covid19hg.org/results/r6/

Table 1 (Continued)

Function	Gene/Locus	Variant	Population	Study design	Sample size	Outcomes	Refs.
Multiple	ACE2	rs190509934	Multiple	COVID-19 infection vs. population	112,612 cases vs. 2,474,079 controls	Associated with susceptibility	https://www.covid19hg.org/results/r6/
Multiple	MUC5B**	rs35705950	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/
Multiple	FOXP4	rs1886814	Multiple	Hospitalized COVID-19 vs. population	24,274 hospitalized cases vs. 2,061,529 controls	Associated with severity	https://www.covid19hg.org/results/r6/

SLC6A20: Solute carrier family 6 member 20, LZTFL1: human leucine zipper transcription factor like 1, CCR9: CC motif chemokine receptor 9, FYCO1: fyve and coiled-coil domain-containing protein 1, CXCR6: C-X motif chemokine receptor 6, XCR1: X-C motif chemokine receptor 1, ABO: ABO gene, IFNAR2: interferon alpha and beta receptor subunit 2, OAS3: 2′−5′-oligoadenylate synthetase 3, DPP9: dipeptidyl peptidase 9, ICAM5/TYK2: intercellular adhesion molecule 5/tyrosine kinase 2, HLA-G: human leukocyte antigen-G, CCHCR1: coiled-coil alpha-helical rod protein 1.

**　The same variant is associated with COVID-19 diagnosis in a candidate gene study (Table 2).

more effectively than SARS-CoV-1, which does not suppress IFN1s and other cytokines like SARS-CoV-2(42). Impaired IFN1 responses were observed in critically diseased patients with persisting high viral loads in blood and uncontrolled inflammation [43]. Consequently, administration of type 1 IFNs has been investigated. A retrospective cohort study reported favorable effects of early administration of IFN-alpha 2b, while later IFN treatment was associated with increased mortality or delayed recovery [44].

IFN1 signaling can be inhibited by glucocorticoids [45,46], which has caused concerns about administration of dexamethasone at early stages of infection. Dexamethasone is not recommended by NIH treatment guidelines in patients not requiring supplementary oxygen [47]. Inhibitory effects of early dexamethasone treatment on viral clearance have been shown during the SARS [48] and MERS [49] outbreaks, lending evidence to the importance of the IFN1 response in containing viral replication during initial infection. Steroid inhalation, on the other hand, has provided benefits in early infections in a randomized trial [50].

2.4. Oligoadenylate synthetases (OAS1, 2, 3)

Association signals in the GenOMICC study are rs10735079 (OAS3) and rs4766664 (OAS1) [16]. OAS genes are interferon-inducible genes in antiviral defense. Upon dsRNA binding, OAS proteins produce the second messenger 2′−5′-linked oligoadenylate (2−5A), which activates ribonuclease L, degrading viral RNA to block viral replication [51]. The HGI reports rs10774671, which is in LD with rs10735079, as a top association with critical illness, hospitalization and SARS-CoV-2 infection, all compared to healthy controls [15]. Two MR studies linked increased OAS1 expression via the intronic rs4767027 SNP in OAS1 to reduced COVID-19 susceptibility and decreased hospitalization risk, confirmed by OAS1 plasma levels in SARS-CoV-2 patients [33,34]. Increased OAS3, conflictingly, was associated with more severe disease [33].

The two SNPs described in the GenOMICC study are part of a distinct OAS1 haplotype which was described with the lead variants rs4767027-T (LD: rs4766664) and rs10774671-G. This haplotype originates from Neanderthals and occurs only in non-Africans. Protective effects of the "Neanderthal haplotype" were shown in West Nile-, Hepatitis C-and SARS-CoV-1 infections [52].. Evidence for the role of this haplotype in COVID-19 has been narrowed down the "Neanderthal haplotype" to a 19 kb-region in OAS1 and examined its in vitro and case-control effects [53]. The haplotype was associated with severe disease protection in 1555 European patients. In functional studies, rs10774671 and rs1131454 regulated OAS1 expression via nonsense-mediated decay of RNA. Nonsense-mediated decay was reduced with the "Neanderthal" haplotype isoform, leading to higher OAS1 levels. OAS1 isoforms did not differ in anti-SARS-CoV-2 activity in vitro, as decrease of viral loads was comparable between cells expressing both isoforms. Interferons could induce both OAS1 isoforms in vitro. In addition, genotyped OAS1 haplotypes were associated with viral clearance in patients treated with interferon. Viral clearance was slower with the risk (non "Neanderthal") haplotype in the placebo-group, but no association was observed among the treatment group, suggesting interferon treatment outweighing genetic OAS1 deficits [53]. This suggests a protective role of interferon-induced and OAS-mediated -degradation in clearing SARS-CoV-2 and avoiding progression to severe disease, as the association with critical COVID-19 was most significant in the GenOMICC and HGI data. Pharmacological strategies to potentiate the effect of OAS1 are anticipated and, in view of the increasing evidence for the role of OAS1, could be considered for repurposing for COVID-19 treatment [33], taking into account a possible adverse role of OAS3. As discussed, interferon treatment at the right timepoint during infection may be beneficial. This might hold especially for patients carrying the risk non-Neanderthal OAS1 haplotype.
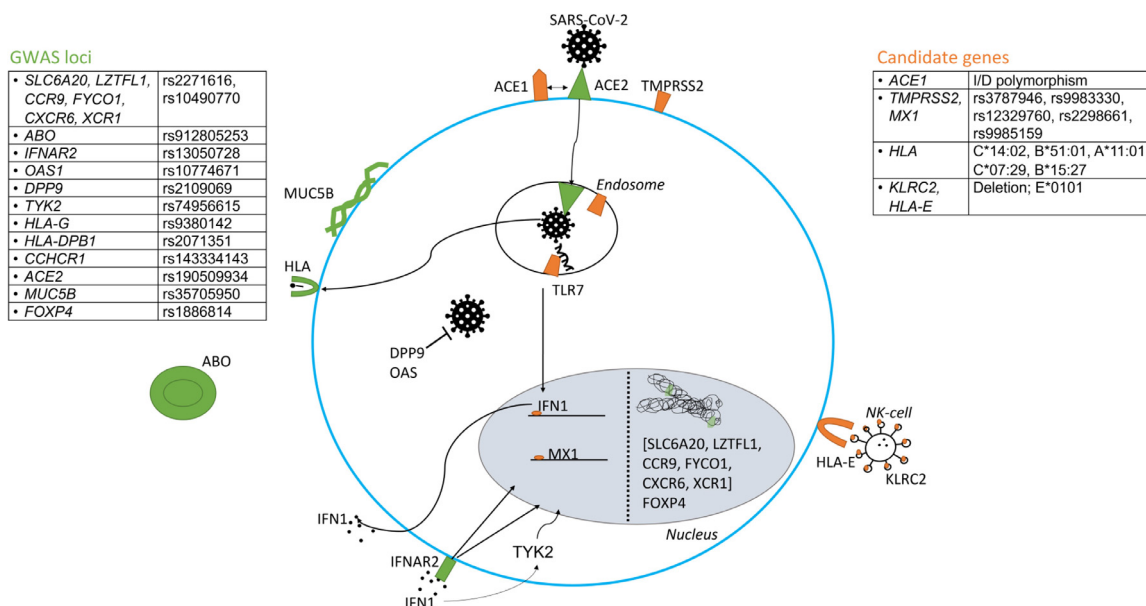
Fig. 1. Host genetic variants and/or genes associated with SARS-CoV-2 infection and COVID-19 severity.

Cell with representation of GWAS and candidate genes; in addition, boxes represent genes with respective variants which were associated with SARS-CoV-2 infection and COVID-19 severity. Genes which were associated in GWAS are represented in green, genes from candidate gene association studies in orange. SLC6A20, solute carrier family 6 member 20; LZTFL1, leucine zipper transcription factor like 1; CCR9, CC motif chemokine receptor 9; FYCO1, fyve and coiled-coil domain-containing protein 1; CXCR6, C-X motif chemokine receptor 6; XCR1, X-C motif chemokine receptor 1; ABO, ABO gene; IFNAR2, interferon alpha and beta receptor subunit 2; OAS3, 2′−5′-oligoadenylate synthetase 3; DPP9, dipeptidyl peptidase 9; TYK2, tyrosine kinase 2; HLA-G, human leukocyte antigen-G; HLA-DPB1, human leukocyte antigen-DPB1; CCHCR1, coiled-coil alpha-helical rod protein 1; ACE2, angiotensin-converting enzyme 2; ACE1, angiotensin-converting enzyme 1; TMPRSS2, transmembrane protease serine 2; MX1, myxoma resistance 1; TLR7, toll like receptor 7; HLA, human leukocyte antigen; KLRC2, killer cell lectin like receptor C2; MUC5B, mucin 5B; FOXP4 Forkhead Box P4 (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

2.5. Dipeptidyl peptidase 9 (DPP9)

DPP9 rs2109069 was associated with severe COVID-19 [16], replicated in the HGI dataset [15]. DPP9 belongs to the S9B/DPPIV serine protease family, and its substrates include CXCL10, CXCL11 and CXCL12 [54], also involved in antigen presentation [55]. CXCL10 and CXCL11 were also induced by SARS-CoV-2 in vitro [42,56]. DPP9 downregulates the inflammasome by maintaining the inflammasome sensor NLRP1 inactive [57]. In a recent GWAS, DPP9 was associated with susceptibility to idiopathic lung fibrosis (IPF) [58]. When looking at association signals at this locus, rs12610495, which is in strong LD with rs2109069, an eQTL in lung tissue for DPP9 led to decreased DPP9 levels, consistent with an increased risk of severe COVID-19 [29,59]. The study also examined lung transcriptome data from COVID-19 patients and found that DPP9 levels were increased compared to controls or patients with bacterial pneumonia.'

2.6. Tyrosine kinase 2 (TYK2)

TYK2 is a Janus kinase required for IFN, IL-12, and IL-23 signal transduction and for T-helper 1/T helper 17 cell-dependent immune responses. Patients with TYK2-deficiency are more susceptible to viral infections. In the GenOMICC GWAS, rs11085727 located close to ICAM5/TYK2 (intercellular adhesion molecule 5/tyrosine kinase 2) was associated with severe COVID-19 [16]. Another TYK2 variant, rs74956615, was also a lead association with hospitalization due to COVID-19 and with critical disease in the HGI analysis [15]. Furthermore, in the GenOMICC study an association of high TYK2 expression with critical COVID-19 was observed, implying a causal role of TYK2 in severe disease [16].

Although TYK2 has come up in two GWAS analyses, deciphering mechanism of action for this signal is difficult. Variant rs74956615, conferring risk of severe COVID-19, is in LD with rs34536443, a known missense variant of TYK2 which reduces its activity and for

which protective effects in at least ten autoimmune diseases have been reported [60]. rs34536443 reduces TYK2-dependent phosphorylation in vitro and in humanized mice, but this was not observed to the same extend as in complete TYK2 deficiency, which is associated with severe recurrent infections [60,61]. rs34536443 was not correlated with hospitalization due to mycobacterial, bacterial, viral, or fungal infections in the UK Biobank. The rs34536443-CC genotype might reduce TYK2-dependent IFN1, IL-12, and IL-23 signaling to an optimum, protecting against autoimmunity without causing immunodeficiency [60]. Therefore, if rs34536443 is the causal susceptibility variant to severe COVID-19 at this locus, this cannot be explained by a general TYK2-dependent immunodeficiency, as suggested in the HGI study [15]. In COVID-19, it is possible that the pronounced suppression of IFN1 signaling observed in SARS-CoV-2 infection adds to the reduced TYK2 function, leaning towards an impaired IFN1-mediated cellular immune response and hinder viral clearance [43]. Alternatively, as the signal at the TYK2 locus overlaps with several genes, other less characterized variants might cause the association.

Placing TYK2's role in COVID-19 at early disease phases, where strong IFN1 responses are required which could be reduced in rs34536443-CC genotype carriers, is at odds with theories suggesting high TYK2-activity as risk factor for CS at later stages. This "hyperinflammation hypothesis" is backed by the observations made in MR and the fact that IL-12, which is involved in CS [6,42], employs TYK2 for signal transduction. It has been argued that baricitinib, a JAK1/2 inhibitor used for treatment of rheumatoid arthritis and atopic dermatitis which inhibits TYK2, has shown promising results in trials for its efficiency in COVID-19 [62,63] and has received an FDA emergency use authorization for treatment of severe COVID-19 [64]. Consequently, COVID-19 treatment guidelines now recommend either baricitinib or tocilizumab together with dexamethasone for severely affected hospitalized patients [65]. It is, however, possible that the beneficial effects of baricitinib result from inhibition of kinases other than TYK2.

2.7. Human leukocyte antigens (HLA)

HLA proteins with increased binding specificity for SARS-CoV-2 peptides are expected to enable more efficient antigen presentation and prompt a more effective adaptive immune response [66]. HLA-G rs9380142 was found associated with critical illness [16]. This variant replicated in the HGI round 5 metanalysis, however, high heterogeneity between studies was observed [15]. Intron variant (rs143334143) in the gene encoding the coiled-coil alpha-helical rod protein 1 (CCHCR1), located in the MHC region close to HLA-C, was associated with critical COVID-19 [16]. In the HGI data release 6, this variant has been replicated in the hospitalization vs. population controls analysis (rs111837807). Additionally, HLA-DPB1 rs2071351 reached genome-wide significance with a p value (4.60E-08) in the susceptibility analysis (https://www.covid19hg.org/results/r6/).

Considering classic HLA antigens, the binding affinity across 145 HLA types for the SARS-CoV-2 proteome in silico was investigated. HLA-A*25:01, B*46:01, and C*01:02 were predicted to bind the fewest peptides, while HLA-A*02:02, HLAB*15:03 and HLA-C*12:03 were top presenters of conserved SARS-CoV-2 peptides [66]. These alleles could represent risk or protective factors for severe courses of the disease, respectively. HLA-B*15:27 was associated with SARS-CoV-2 infection in the analysis of 82 Chinese donors of SARS-CoV-2 convalescent plasma compared to 3548 controls [67]. An association study investigating the severity of COVID-19 in Chinese patients found HLA-C*14:02, B*51:01 and A*11:01 associated with severity. No association with HLA-B*46:01 was observed [68].

2.8. Angiotensin-converting enzyme 2 (ACE2)

ACE2 is a membrane-bound receptor highly expressed in the lung, heart, kidney, endothelia, and gastrointestinal tract. It cleaves angiotensin II to angiotensin $1-7$ (Ang$1-7$). SARS-CoV-2 binds to ACE2 as a cell entry receptor via the receptor binding domain (RBD) of the viral spike protein (S-protein) [69]. A recent meta-analysis by Horowitz et al. and the HGI using GWAS studies concluded that the ACE2 variant (rs190509934:C; a rare X-linked variant) reduces the risk of SARS-CoV-2 infection, but not the severity [70]. Horowitz et al., additionally used RNA sequencing data, concluded that ACE2 expression is lower in individuals carrying the C allele [70] and postulated that ACE2 expression may be partially protective against SARS-CoV-2 infection.

Previously, it was discussed whether high ACE2 expression poses a risk of severe disease, as more receptors are available for virus entry, or might rather be protective, as increased ACE2 activity has been linked to anti-inflammation and protection from cardiovascular disease [71,72]. In COVID-19, a decrease in ACE2 levels is observed, favoring inflammation and thrombosis [73]. Therefore, high ACE2 levels might be desirable, especially during the CS. A recent MR study pointed towards supplementation of human recombinant soluble ACE2 (hrsACE2) as potential target for drug repurposing. HrsACE2 would likely influence both effects of ACE2. First, hrsACE2 binds the S-protein and could diminish viral uptake. Second, it cleaves angiotensin II thus exerting anti-inflammatory effects, which is most relevant in later stages of the disease [41]. However, if further characterization of the protective GWAS-significant rs190509934 variant proves its negative effect on ACE2 expression, especially in lung tissue, this will lend evidence to a benefit of less cell entry receptors at the beginning of the infection. Still, it is possible that supplementing hrsACE2 during the hyperinflammatory stage can improve the anti-inflammatory response.

Other polymorphisms affect the ACE1-ACE2 balance, increasing angiotensin II and counteracting protective effects of Ang$1-7$. An insertion/deletion (I/D) in the ACE1 gene (previously rs4646994) has been shown to increase the risk of hypertension, cardiovascular and respiratory disease, as homozygous carriers of the D allele (D/D) have

the highest ACE1 levels compared to the I/D and I/I genotypes. The I/D genotype was found associated with ARDS [74] and severity of SARS [75]. However, candidate gene studies investigating the I/D polymorphism showed conflicting results. The ACE1 I/D polymorphism and rs2285666 of ACE2, another risk factor for hypertension and heart failure, in 204 COVID-19 patients and 536 matched controls were studied. The D/D genotype was associated with disease severity, but not with susceptibility to infection per se, and became insignificant after multivariate logistic regression. No differences were observed for ACE2 rs2285666 [74]. In contrast, in a Czech cohort of 410 SARS-CoV-2 patients, genotype I/I of ACE1 was enriched in symptomatic patients [76].

2.9. Mucin 5B (MUC5B)

In the most recent metanalysis by the HGI (https://www.covid19hg.org/results/r6/), an association of MUC5B rs35705950 with hospitalization due to COVID-19 was reported. rs35705950 is a promoter polymorphism described as the most important genetic risk variant for IPF [58]. The high-expressing T-allele, which is a risk factor for IPF, was protective. As mucins belong to the first defense against pathogens in the airways and essential for mucociliary clearance, high expression may protect against SARS-CoV-2 infection [77]. This association was partially replicated in a study investigating the shared genetic background for IPF and COVID-19. A protective effect of rs35705950T was also observed, while all other risk variants of IPF increased the risk of COVID-19. However, there may have been selection bias, as IPF patients are likely to self-isolate and protect themselves from SARS-CoV-2 infection. Therefore, carriers of the T-allele might be underrepresented in the COVID-19 patients population [78]. This could, of course, also effect the HGI study.

2.10. Forkhead box P4 (FOXP4)

The HGI GWAS metanalysis demonstrated the association of rs1886814 in the transcription factor FOXP4 with hospitalization [15]. Interestingly, this SNP is in LD with an IPF variant rs2894439 in European ancestries, which reduces FOX4 expression in lung tissue in IPF cases compared to controls [79]. FOXP4 is a developmental protein in the airway epithelium and important in epithelial regeneration. Knockdown of FOXP4 and FOXP1 can disenable epithelium regeneration in lung tissue [80]. FOXP4 is necessary for normal T-cell recall responses [81].

2.11. Clinical implication of the GWAS loci

Several GWAS loci overlap with loci previously associated with lung-related phenotypes (MUC5B, FOXP4) of autoimmune/inflammatory diseases in immunoregulatory pathways (TYK2, IFNAR2, cytokine genes at 3p21.31), or cellular antiviral defense (DPP9, OAS genes). ABO was shown to indirectly influence cytokine levels and an alternative cell entry receptor of SARS-CoV-2. When studied in more detail, the genes may be of importance in identifying molecular mechanisms of COVID-19 pathogenesis, enabling repurposing of existing drugs. Already, the known genetic variants can confirm the prominent role of IFNs in the early defense against infection and point towards inflammatory pathways involved in the CS. Some of the genes have been reported to represent targets of drugs in use against COVID-19, mainly dexamethasone, but also baricitinib.

Genetic data has enabled the development of polygenic risk scores (PRSs) for complex diseases (www.pgscatalog.org/), including COVID-19 [70,82–84]. A PRS is a calculated estimate of traits or disease susceptibility according to individual genetic profiles based on GWAS summary statistics. It is known that the effects of individual GWAS variants are small; a combination of many genetic variants in a polygenic risk score, however, explains a larger portion of the risk. Some

studies have now generated risk scores to predict COVID-19 severity using GWAS data generated by international collaborations [70,82−84]. Some risk scores apparently predict severe COVID-19 reliably, allowing for identification of high-risk individuals who should be prioritized for vaccination, preventive measures and behavioral changes. However, further studies are needed to enable the use of genetic markers for risk stratification and prediction of COVID-19 courses and outcomes.

3. Variants associated with COVID-19 in candidate gene studies

Candidate genes with possible relevance to COVID-19 pathogenesis have been investigated (Table 2, Fig. 1). These include genes involved in cell entry as well as several immunological genes, but also genes linked to diseases like dementia or cystic fibrosis.

3.1. Cell entry: transmembrane protease serine 2 (TMPRSS2)

Unlike SARS-CoV-1, SARS-CoV-2 is cleaved for cell entry by host proteases. The S-protein undergoes two cleavage steps before membrane fusion. First, it is cleaved between the S1 and S2 domains by the host-cell proteases TMPRSS2 and furin. Second, the protein is cleaved in the S2 domain to allow membrane fusion. This can occur either at the plasma membrane by use of TMPRSS2 or in the endosome by cathepsin L [85]. Variants of TMPRSS2 and the nearby MX1 (myxoma resistance 1) gene in the HGI hospitalization metanalysis of European COVID-19 patients were explored [86]. MX1 is an antiviral effector protein with a broad specificity, including RNA and DNA viruses. It is not expressed constitutively but induced by type I (alpha/beta) and III (lambda) IFNs. Three association signals on chromosome 21 were identified, including rs3787946 in TMPRSS2,

Table 2
Candidate gene studies on COVID-19.

Function	Gene/Locus	Variant	Population description	Study design	Sample size	Outcomes	Refs.
Cell entry related genes							
Cell entry	ACE1*	I/D polymorphism	Spanish	Hospitalized patients vs. controls	204 hospitalized patients (67 severe) vs. 536 controls	D/D genotype associated with COVID-19	[74]
Cell entry	ACE1*	I/D polymorphism	Czech	Recovered patients vs. controls	410 recovered patients (164 symptomatic vs. 2579 controls	I/I genotype associated with COVID-19	[76]
Protease/ Cell entry	TMPRSS2; MX1	rs3787946, rs9983330; rs12329760, rs2298661, rs9985159	European	Hospitalized patients vs. controls	6406 hospitalized vs. 902,088 controls	Associated with hospitalization and increased MX1 expression in blood	[86]
Genes of the innate and adaptive immunity							
Innate	TLR3, UNC93, TICAM, TBK1, IRF3, IRF7, IFNAR1, IFNAR2	Deleterious rare variants	Multiple	Critical COVID-19 vs. asymptomatic	659 critical vs. 534 mild/asymptomatic patients	Associated with critical COVID-19 and low IFN1-levels	[17]
Innate	TLR3, IRF7, IRF9, TICAM1/TRIF, UNC93, TRAF3, TBK1, IRF3, NEMO/ IKBKG, IFNAR1, IFNAR2, STAT1, STAT2	Deleterious rare variants	Multiple	Severe COVID-19 vs. mild and vs. controls	1864 COVID-19 cases (713 with severe and 1151 with mild disease) and 15,033 controls	No association with severe COVID-19 or SARS-CoV-2 infection.	[111]
Innate	TLR7	Deleterious rare variants	African and Dutch	Genetic and immunological phenotype	2 brother pairs	Associated with decreased IFN-γ production	[109]
Innate	TLR7	Deleterious rare variants	Italian	Critical COVID-19 vs. asymptomatic	135 critical vs. 104 asymptomatic patients	Associated with critical COVID-19 and downregulated type I IFN-signaling in a subset of variants	[110]
Innate and adaptive	HLA	HLA-C*14:02, HLA-B*51:01, HLA-A*11:01	Chinese	COVID-19 severe vs. mild	323 hospitalized patients	Associated with severity	[68]
Innate and adaptive	HLA	HLA-C*07:29, HLA-B*15:27	Chinese	COVID-19 patients vs. controls	82 patients vs. 3548 controls	Associated with susceptibility to infection	[67]
Innate	KLRC2; HLA-E	Deletion; HLA-E*0101	Austrian	Patients vs. controls, ICU vs. non-ICU	190 hospitalized patients vs. 92 non hospitalized vs. 260 controls	Associated with hospitalization	[112]
Innate	MUC5B**	rs35705950	Dutch	Hospitalized patients vs. controls	108 patients vs 611 controls	Associated with COVID-19	[77]

ACE2: angiotensin-converting enzyme 2, ACE1: angiotensin-converting enzyme 1, TMPRSS2: transmembrane protease serine 2, MX1: myxoma resistance 1, TLR3: toll like receptor 3, UNC93B: unc-93 homolog b1, TICAM1: toll like receptor adaptor molecule 1, TBK1: tank binding kinase 1, IRF3: interferon regulatory factor 3, IRF7: interferon regulatory factor 7, IFNAR1: interferon alpha and beta receptor subunit 1, IFNAR2: interferon alpha and beta receptor subunit 2, TLR7: toll like receptor 7, HLA: human leukocyte antigen, KLRC2: killer cell lectin like receptor C2, MUC5B: mucin 5B.

* ACE1 regulates expression of ACE2 and is therefore listed in the cell entry section, although it is not involved in cell entry itself. The ACE2 polymorphism is listed in the GWAS (Table 1).

** The same variant is associated with COVID-19 severity in GWAS (Table 1).

adjacent to *MX1*. Five variants in high LD were identified at this *TMPRSS2/MX1* locus and associated with a reduced risk of hospitalization and with increased MX1 expression. One variant, rs12329760, is a coding variant of *TMPRSS2* (*p*.Val197Met). Confirmation studies of the association in the GenOMICC study showed that all five SNPs could be replicated in two Asian cohorts, while two SNPs replicated in patients of African ancestry [86]. In the HGI data release 6, this LD block reached the threshold of $p = 10^{-5}$ for a suggestive signal in critical illness as well as the hospitalization analysis. Consistently, the genotype showed a trend towards protection from severe disease.

Increased MX1 levels have been observed in COVID-19 patients. MX1 was proposed as a critical component of antiviral defense [87]. Therefore, a generally increased expression of the protein could be protective. Additionally, promotor polymorphisms which influence MX1 expression levels have been put forward in SARS association studies [88−90].

Male sex in COVID-19 has raised the question of whether sex hormones such as androgens might influence the severity. The expression of TMPRSS2 is upregulated by the androgen receptor (AR) [91,92]. A case-control study analyzed the length of a polyglutamine tract (polyQ) within the X-linked androgen receptor (AR) gene in male COVID-19 patients, replicating a previous observation [93]. The longer these polyQ repeats, the lower the receptor activity and thus the biological effect of testosterone. The authors demonstrated that long polyQ alleles are associated with disease severity and show a trend towards higher inflammatory markers [94]. One conceivable mechanism for this association is the known attenuation of inflammatory responses by testosterone, which may be less efficient in patients with long polyQ alleles [94]. In a small cohort of 31 patients, low testosterone levels were also associated with the severity of COVID-19 infection [95]. In a retrospective study examining clinical data from 4532 men who tested positive for SARS-CoV-2, it was found that prostate cancer patients who received androgen deprivation therapy had a lower risk of infection than other prostate cancer patients, suggesting a protective effect of low testosterone [96]. Furthermore, it was recently shown that TMPRSS2 expression shows no sex differences in lung tissue [97] and is also not regulated by the AR in the lung [98]. Given the genetic evidence for a role of the AR and testosterone in COVID-19, a functional characterization of the effects of androgens during infection must follow.

3.2. Genes of the innate and adaptive immunity

Cytokines are important in regulating the host immune response, but in severe COVID-19 they can cause hyperinflammation and CS. Thus, variants influencing the expression of cytokines could be relevant to COVID-19. Furthermore, as the importance of effective interferon responses against SARS-CoV-2 has been shown, deleterious variants of genes along this pathway have been targeted in candidate gene studies, among other immunological genes like interferon-induced genes and complement components.

3.2.1. Variants of cytokine genes

During the clinical course of COVID-19, especially severe COVID-19, the cytokines interferons, interleukins, lymphokines and tumor necrosis factors (TNFs) are involved in immune dysregulation and a CS, which impedes the clearance of the SARS-CoV-2 virus [6,7]. Cytokines, especially interleukin-6 (IL-6), interleukin-1beta (IL-1beta), CXCL10, TNF, interferon-gamma, macrophage inflammatory protein (MIP) 1alpha and 1beta and VEGF are elevated in severe COVID-19 patients [7]. High IL-6 levels are significantly associated with poor treatment outcome, and suppression of the cytokine storm by glucocorticoids, immunomodulators, cytokines and cytokine receptor antagonists has led to better treatment outcome [6].

CS occurs in critical COVID-19 [99−101]. Elevated IL-6 levels also play a role in inflammatory responses in Kawasaki disease [102].

Although no association studies found an association between *IL-6* polymorphisms and disease severity, a polymorphism associated with pneumonia was suggested as risk variant. *IL-6* rs1800795, was significantly associated with pneumonia severity and higher IL-6 levels [103]. Moreover, the *IL-4* rs2070874 SNP could be relevant to COVID-19 severity, as it was associated with respiratory tract infection in a metanalysis of 386 association studies [104]. The same polymorphism was found to be associated with Kawasaki disease in Iranian children [105].

Tocilizumab is a humanized monoclonal antibody that blocks the IL-6 receptor, thereby inhibiting IL-6 mediated signaling. Tocilizumab is licensed for the treatment of CS. Two trials, the Randomized Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia (REMAP-CAP) [106] and the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial [107] have investigated the use of tocilizumab in ICU COVID-19 patients. Both trials found a reduction in mortality, leading to the recommendation of administering tocilizumab within 24 h of ICU admittance together with dexamethasone [47]. Other monoclonal antibodies directed against IL-6 under investigation include clazakizumab, sarilumab, and siltuximab [108]. Pirfenidone, suggested also as treatment option, inhibits IL-1 beta and IL-4 [108]. As a broader anti-inflammatory treatment, dexamethasone is recommended for all patients requiring oxygen support and progressed to dysregulated inflammatory response [47].

3.2.2. Genes of the interferon type 1 pathway

Genes of the IFN1 pathway have been studied in candidate gene studies to identify loss of function mutations (LOF), explaining severe courses. The study of two brother pairs from unrelated families with inborn defects of the X-chromosomal *TLR7* was described. All patients suffered from severe disease at a young age [109]. This was recently replicated in a WES study which compared male COVID-19 patients with an age below 60 years and requiring mechanical ventilation, compared to mild cases who were not hospitalized. Rare *TLR7* deleterious variants were enriched among severe cases (2.15% of cases, none in controls) and most of the variants affected protein function *in vitro*. Since not all variants were functionally active, the true percentage of TLR7 deficiency could be slightly lower in young males [110]. A case-control study looked at 13 genes involved in IFN1 responses in 659 COVID-19 patients and identified LOF mutations in eight of these genes (*TLR3, UNC93B, TICAM1, TBK1, IRF3, IRF7, IFNAR1, IFNAR2*). The variants were associated with low IFN-alpha levels and life-threatening COVID-19 [17].

A WES/WGS study with 1864 COVID-19 cases and 15,033 controls attempted to replicate these findings. No enrichment of LOF variants in the 13 candidate genes proposed in the original study was found. In fact, only one severe COVID-19 patient carried a LOF mutation, p. Arg330* in STAT2 [111].

3.2.3. Killer cell lectin like receptor C2 (KLRC2), HLA-E

NKG2C, encoded by *KLRC2*, is an activating receptor of natural killer (NK) cells involved in antiviral responses in the lungs. Its cellular ligand is HLA-E, which mediates cytotoxic and proinflammatory NK cell responses. *KLRC2* deletion is associated with decreased or absent expression of the NKG2C receptor. HLA-E*0101 and HLA-E*0103 are the commonest variants of the cellular ligand in Europe. A recent candidate gene study found an association between NKG2C deletion and the HLA-E*0101 allele with risk of hospitalization and ICU admission in COVID-19 patients. This is in line with the observation of reduced NK cell counts and increased expression of inhibitory receptors on NK cells in COVID-19 patients [112].

Outstanding questions. Research has meanwhile gathered a wealth of information on the role of host genetic factors in COVID-19 at an impressive pace. This was possible because of the vast amount of genetic data available from UK Biobank, 23andMe, AncestryDNA and

other multinational collaborators. We have addressed GWAS loci, candidate gene variants, and LOF variants that may be important in specific disease traits, especially cell entry of SARS-CoV-2, inflammation, and CS, but also in innate and adaptive immunity. We have discussed mechanisms and signaling pathways in disease development and genes that are considered targets for drug development and repurposing.

Studies have linked genetic variants to molecular phenotypes such as plasma proteins or inflammatory markers, by measuring protein levels in patients, using transcriptomics data, or by MR. All approaches may improve the understanding of mechanisms in SARS-CoV-2 infection. Bioinformatically integrating multi-omic datasets such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, or microbiomics will fill gaps in our understanding of COVID-19 in the future.

Research on PRS has been growing rapidly. Several scores have been proposed to predict COVID-19 susceptibility/and severity. PRSs can provide important public health advice during pandemics by allowing identification of high-risk individuals. Clearly, all associations described must be interpreted with caution, in particular with regard to clinical decisions and the need to be evaluated in functional studies, including all ethnic groups.

Search strategy and selection criteria. We searched PubMed and the LitCovid database (search string (host gene*[Title/Abstract]) AND (COVID-19[Title/Abstract] OR SARS-CoV-2[Title/Abstract]) until August 2021. We also considered SNPs observed in metanalyses to be associated with pneumonia/respiratory tract infection. Case-control studies, case reports, case-control metanalyses, and *in vitro* validation studies confirming associations between SNPs and disease phenotypes are included to provide a list of variants associated with COVID-19.

Declaration of Competing Interest

All authors declare no competing interests.

Acknowledgments

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