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REVIEW

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Interindividual immunogenic variants: Susceptibility to coronavirus, respiratory syncytial virus and influenza virus

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Summary

The coronavirus disease (Covid-19) pandemic is the most serious event of the year 2020, causing considerable global morbidity and mortality. The goal of this review is to provide a comprehensive summary of reported associations between interindividual immunogenic variants and disease susceptibility or symptoms caused by the coronavirus strains severe acute respiratory syndrome-associated coronavirus, severe acute respiratory syndrome-associated coronavirus-2, and two of the main respiratory viruses, respiratory syncytial virus and influenza virus. The results suggest that the genetic background of the host could affect the levels of proinflammatory and anti-inflammatory cytokines and might modulate the progression of Covid-19 in affected patients. Notably, genetic variations in innate immune components such as toll-like receptors and mannose-binding lectin 2 play critical roles in the ability of the immune system to recognize coronavirus and initiate an early

Abbreviations: AHSG, alpha 2-HS glycoprotein; C3, complement molecule C3; C5, complement molecule C5; CCL2, C-C motif chemokine ligand 2; CCL5, C-C motif chemokine ligand 5; CCR5, C-C motif chemokine receptor 5; CD14, cluster of differentiation 14; CD209, cluster of differentiation 209; CD55, complement decay-accelerating factor; CLEC4M, C-type lectin domain family 4 member; Covid-19:, coronavirus 2019 disease; CX3CR1, C-X3-C motif chemokine receptor 1; CXCL9, C-X-C motif chemokine receptor 6; CXCR6, C-X-C motif chemokine receptor 6; DC, dendritic cell; FCGR2A, Fc fragment of IgG receptor 2A; FcR, Fc (fragment crystallizable) receptor; H1N1, influenza A virus subtype H1N1 (A/H1N1); H3N2, influenza A virus subtype H3N2 (A/H3N2); HIV, human immunodeficiency virus; HLA, human leukocyte antigen; ICU, intensive care unit; IFITM3, interferon induced transmembrane protein 3; IFN, interferon; IFNA5, IFN alpha 5; IFNAR1, IFN alpha and beta receptor subunit 1; IFNAR2, IFN alpha and beta receptor subunit 2; IFNG, IFN gamma; IFNL3, IFN lambda 3; IL, interleukin; IL10, interleukin 10; IL12A, interleukin 12A; IL12RB, interleukin 12 receptor beta 1 subunit; IL13, interleukin 13; IL17A, interleukin 17A; IL18, interleukin 18; IL19, interleukin 19; IL1A, interleukin 1 alpha; IL1B, interleukin 1 beta; IL1RL1, interleukin 1 receptor like 1; IL20, interleukin 20; IL27, interleukin 27; IL4, interleukin 4; IL4R, interleukin 4 receptor; IL5, interleukin 5; IL6, interleukin 6; IL7, interleukin 7; IL9, interleukin 9; IRF, IFN regulatory factor; LD, linkage disequilibrium; LOF, loss of function; LRTI, lower respiratory tract infection; MBL2, mannose-binding lectin 2; MX1, MX dynamin like GTPase 1; NSP1, nonstructural protein 1; OAS1, 2′-5′-oligoadenylate synthetase 1; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome; SARS-CoV, severe acute respiratory syndrome-associated coronavirus; SARS-CoV-2, severe acute respiratory syndrome-associated coronavirus-2; SNP, single nucleotide polymorphism; TLR, toll-like receptor; TNF, tumor necrosis factor; TNFRSF1B, tumor necrosis factor receptor superfamily member 1B.

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immune response to clear the virus and prevent the development of severe symptoms. This review provides promising clues related to the potential benefits of using immunotherapy and immune modulation for respiratory infectious disease treatment in a personalized manner.

KEYWORDS
Covid-19, cytokine storm, genetic susceptibility, influenza virus, immune-related variants, RSV

1 | INTRODUCTION

The recent global coronavirus disease 2019 (Covid-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is the defining global health crisis. Covid-19 shows a wide range of disease severity among affected individuals from asymptomatic carriers to patients who have severe respiratory failure. While the details of the clinical picture of the Covid-19 pandemic are being increasingly clarified, there remain considerable unanswered questions regarding the role of host genetic background in the susceptibility and vulnerability to SARS-CoV-2 infection.[1]

Valuable genetic susceptibility insight into immunity-related genes has been previously gained from the widespread respiratory viruses such as the respiratory syncytial virus (RSV) and influenza virus. On the other hand, association studies concerning the earlier strain of coronavirus, namely SARS-CoV, could provide some clues since SARS-CoV-2 has 78% genetic identity to SARS-CoV. Regarding the dysfunction of the immune response to Covid-19, two scenarios have been proposed: (1) the immune response is insufficient to clear the virus and prevent the development of severe disease resulting from various factors such as deficiencies in virus recognition and misdirection of antigen presentation; (2) an overactive immune system due to genetic predisposition to immune dysregulation may induce an immunopathological condition named 'cytokine storm' resulting in collateral damage to neighboring tissue, organ failure, and even death.[2–4] Notably, the immune-related genetic susceptibility plays considerable roles in both scenarios. However, the dynamic and complex nature of the immune response during acute infection is still not fully understood. In this review, we focus on the host genetic variations involved in both scenarios in the context of respiratory viruses, with particular emphasis on coronavirus.

2 | PATHOGEN RECOGNITION, PRESENTATION AND ELIMINATION

The innate immune system establishes the first line of host defense during infection through early recognition of pathogens and subsequently induction of proinflammatory responses. On the other hand, the elimination of pathogens in late infection and generation of immunological memory is arranged by the adaptive immune system.

Several genetic variants in the immune system compartments, which influence either the protein structure or expression, have been uncovered and shown to be implicated in human respiratory tract infections (Table 1).

2.1 | Mannose-binding lectin 2

Mannose-binding lection 2 (MBL2) is a soluble, Ca^{2+}-dependent serum protein that is expressed primarily in the liver and secreted into the blood. MBL2 is a vital component of the innate immune response that provides a front line of host defense.[5] Genetic deficiency of *MBL2* gene boosts susceptibility to viral and bacterial agents such as human immunodeficiency virus (HIV), influenza A and *Neisseria meningitides*.[6–8]

2.1.1 | Relevance to coronavirus

The differences in the vulnerability of individuals to the coronavirus infections have been proposed to be linked to the key role of MBL2 in early host defense mechanisms, especially before producing specific antibodies.[9] Polymorphisms in the promoter (rs7096206, C/G) and exon 1 (rs1800450, G/A) have a significant association with SARS-CoV susceptibility.[10,11] Moreover, the alleles associated with low expression of *MBL2* are increasingly present in patients with other respiratory infectious diseases, such as invasive pneumococcal disease[12] and chronic obstructive pulmonary disease.[13,14]

2.2 | Type C lectin

Dendritic cells (DCs) express pattern recognition receptors, such as CD209 and CLEC4M that directly recognize a wide range of microorganisms, for example, hepatitis C, HIV, SARS-CoV-1 coronavirus, and Ebola. Human CD209 and CLEC4M proteins are a C-type lectin, which comprises a Ca^{2+}-dependent complementarity-determining region followed by a flexible neck region at the C-terminal domain, a transmembrane domain and a cytoplasmic N-terminal region.

The extended neck region in the extracellular domain is encoded by tandem repeats, which is involved in the recognition of pathogens.[15]

TABLE 1 Summary of studies which reported the pathogen recognition-, presentation- and elimination-related genetic variants behind the susceptibility and vulnerability to coronavirus, respiratory syncytial virus and influenza

Gene	Variant	Virus	Country	Allele/genotype effect
Pathogen recognition, presentation and elimination				
CD14	rs2569190	SARS-CoV-1	China	CC genotype/risk
CD209	rs4804803	SARS-CoV-1	China	G allele/protective
CD55	rs2564978	Influenza	China	TT genotype/risk
CLEC4M	rs71179137	SARS-CoV-1	China	Homozygous for indel/protective
FCGR2A	rs1801274	SARS-CoV-1	China	GG genotype/risk
HLA	HLA-B*0703	SARS-CoV-1	China	Risk
	HLA-DRB1*0301	SARS-CoV-1	China	Risk
	HLA-DRB1*12	SARS-CoV-1	Vietnam and China	Risk
	HLA-DRB4*01010101	SARS-CoV-1	China	Risk
	HLA-B*4601	SARS-CoV-1	Taiwan	Risk
	HLA-Cw*0801	SARS-CoV-1	Taiwan	Risk
	HLA-B*46:01	SARS-CoV-2	In silico analysis	Risk
	HLA-B*15:03	SARS-CoV-2	In silico analysis	Protective
	Haplotype HLA-A*:01:01 -B*08:01 -C*07:01 -DRB1*03:01	SARS-CoV-2	Italy	Risk
	Haplotype HLA-A*02.01 -B*18.01 -C*07.01 -DRB1*11.04	SARS-CoV-2	Italy	Protective
IRF3	p.Glu49del	SARS-CoV-2	Bolivian/Spain	Heterozygote for TCC deletion/risk
	p.Asn146Lys	SARS-CoV-2	Italy	C allele/risk
IRF7	p.Arg7fs	SARS-CoV-2	Italy	C allele/risk
	p.Phe95Ser	SARS-CoV-2	Turkey	G allele/risk
	p.Pro246fs	SARS-CoV-2	Spain	Heterozygote for 13-bp deletion/risk
	p.Pro364fs	SARS-CoV-2	Italy	Homozygote for insertion C/risk
	p.Arg369Gln	SARS-CoV-2	Italy	T allele/risk
	p.Gln185*	SARS-CoV-2	France	A allele/risk
	p.Met371Val	SARS-CoV-2	Turkey	CC genotype/risk
MBL2	rs7096206	SARS-CoV-1	China	C allele/risk
	rs1800450	SARS-CoV-1	China	A allele/risk
TLR3	p.Ser339fs	SARS-CoV-2	Spain	Heterozygote for deletion T/risk
	p.Pro554Ser	SARS-CoV-2	Italy	T allele/risk
	p.Met870Val	SARS-CoV-2	Colombian/Spain	G allele/risk
	p.Trp769*	SARS-CoV-2	Italy	A allele/risk
TLR4	rs4986791	Influenza	Greece	C allele; CC genotype/risk
TLR7	c.2129_2132del	SARS-CoV-2	A family in Netherlands	Frameshift deletion/risk
	c.2383G>T	SARS-CoV-2	A family in Netherlands	T allele/risk

2.2.1 | Relevance to coronavirus

A genetic-risk association study revealed that homozygosity of the rs71179137 variant in *CLEC4M* tandem repeat plays a protective role for SARS-CoV infection.[16] However, this finding has not been approved by a case-control study in northern China.[17] The G allele of the rs4804803 polymorphism located on the *CD209* promoter is associated with low promoter activity.[18] It has been suggested that the G allele could protect the lung from injury during the progression of SARS-CoV infection[19] and patients with the AA genotype had a 60% chance for developing severe symptoms.[18] In contrast, another study among 181 SARS patients and 172 controls reported that no genetic predisposition allele in the lectin genes cluster at 19p13.3 is involved in SARS-CoV-1 infection.[20]

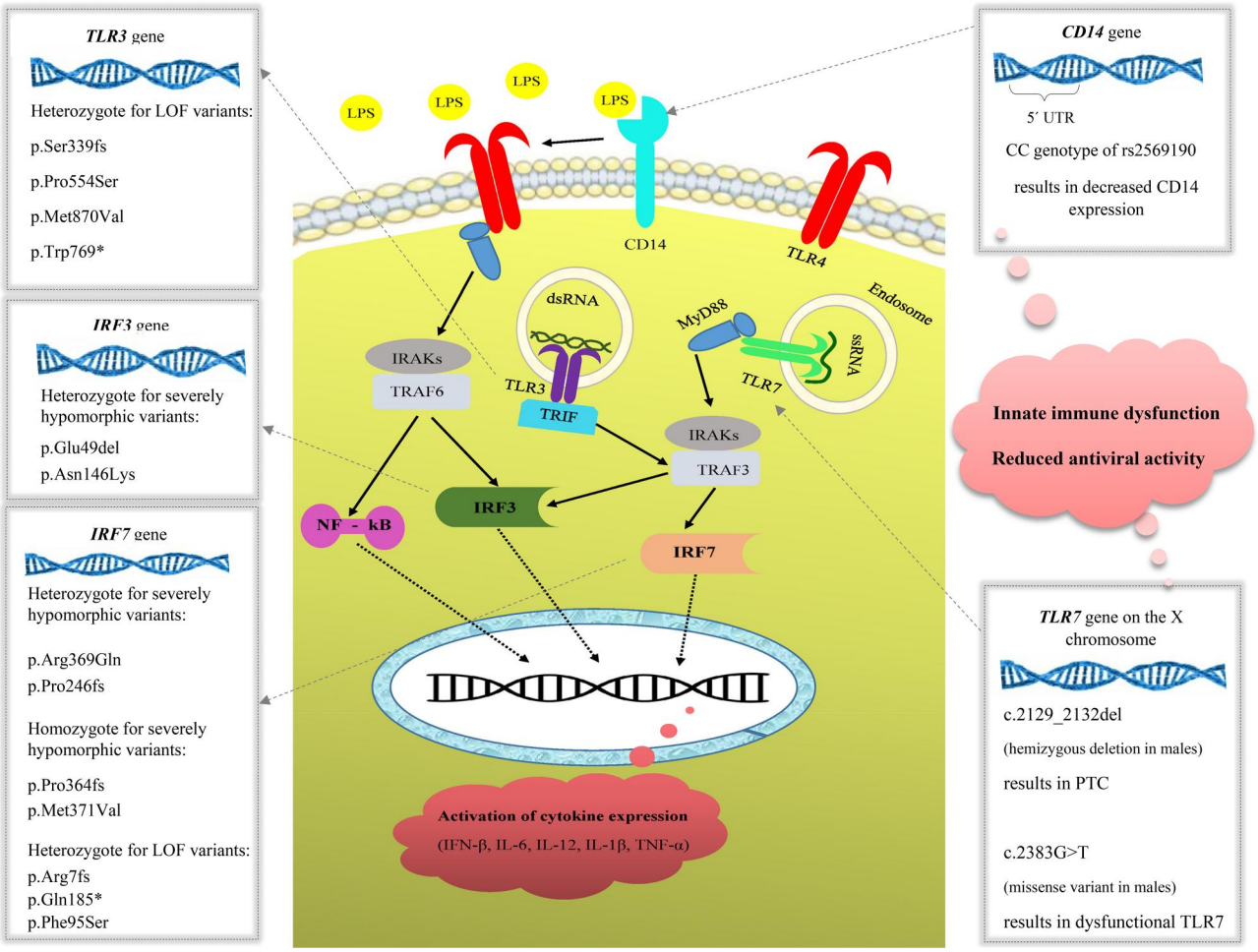

FIGURE 1 Toll-like receptor (TLR) signaling and coronavirus susceptibility. dsRNA, double-stranded RNA; IL, interleukin; IRF, interferon regulatory factor 3; LPS, lipopolysaccharides; NF-κB, nuclear factor kappa B; PTC, premature termination codon; TNF, tumor necrosis factor; ssRNA, single-stranded RNA

2.3 | Toll-like receptor signaling compartments

Toll-like receptors (TLRs) are type I transmembrane glycoproteins expressed by various immune cells such as DCs, macrophages, natural killer cells, and neutrophils as well as epithelial and endothelial cells.[21] Moreover, B and T cells also express the restricted types of TLRs (TLR2, TLR7 and TLR9). These receptors play a pivotal role in the innate immune response by recognizing structurally conserved molecules derived from pathogens.[22]

2.3.1 | Relevance to coronavirus

Early in the process of SARS-CoV-2 infection, the ssRNA and dsRNA structure of the virus is, respectively, recognized by TLR7 and TLR3 in the respiratory tract, which results in inducing proinflammatory cytokines and interferons (IFNs)[23] (Figure 1).

Sequencing methods applied to young males without any underlying diseases from two independent families who showed the severe form of Covid-19 have revealed that rare mutations in *TLR7* could be associated with severe symptoms and even death.[23] The four-nucleotide hemizygous deletion (c.2129_2132del) in the *TLR7* gene, which is likely to generate a premature termination codon, was detected in two severely affected brothers (29 and 32 years old) and their uninfected mother with the heterozygous state, a condition consistent with X-linked inheritance. In a second family, a missense variant (c.2383G>T; p.Val795Phe), which was predicted as deleterious in all in silico prediction tools, was identified in two brothers, age 21 and 23 years, with severe Covid-19 complicated by pulmonary embolisms requiring mechanical ventilation in the intensive care unit (ICU).

Four heterozygote loss of function (LOF) variants in *TLR3* (p.Ser339fs, p.Pro554Ser, p.Trp769* and p.Met870Val) in patients with life-threatening Covid-19 pneumonia was found[24] and some rare variants in *IRF3* and *IRF7* genes have been reported (Table 1).

CD14 is a glycosylphosphatidylinositol-anchored receptor known to serve as a coreceptor for several TLRs both at the cell surface and in the endosomal compartment, which plays a unique role in initiating innate immunity through TLRs-mediated cytokine response.[25]

A possible functional role of the *CD14*-c.159T/C polymorphism (rs2569190) in determining the course of SARS development has

been reported in Chinese patients.[26] It is suggested that *CD14*-c.159CC carriers may have reduced antiviral activity that results in enhanced viral toxicity.

2.3.2 | Relevance to RSV

Investigation of *TLR4* single nucleotide polymorphisms (SNPs) including rs4986790 and rs4986791 in a group of hospitalized infants with severe RSV infection (case group) and two control groups demonstrated an overrepresentation of both *TLR4* SNPs in the case group compared to controls. Therefore, these SNPs were associated with a severe RSV bronchiolitis.[27] Another study on high-risk infants and young children showed that the same SNPs were strongly associated with symptomatic RSV infection[28] while in other populations, either one or both of these SNPs demonstrated marginal[29] or no association with severe RSV disease.[30,31] The rs5743836 SNP in the promoter of *TLR9* was weakly associated with severe RSV,[32] and *TLR9* rs352162 SNP was associated with the requirement for mechanical ventilation. Furthermore, rs352162 and rs187084 SNPs were associated with ICU admission.[33] As for *TLR10*, haplotype analysis demonstrated a weak yet significant association with RSV infection even though no single SNP was identified as the major polymorphism contributing to this demonstration.[32]

2.3.3 | Relevance to influenza virus

Investigation of *TLR4* polymorphisms in individuals infected with the influenza virus revealed that these polymorphisms confer protection in the tonsils against *Haemophilus influenzae*. In addition, there was an association between the rs4986791 SNP and reduced risk of infection with *H. influenzae*.[34]

2.4 | Human leukocyte antigen

The human leukocyte antigens (HLA), which are critical components of the viral antigen presentation pathway, consist of the most polymorphic genes (Figures 2 and 3). They have been shown in various reports to confer differential viral susceptibility and severity of disease. The associations between HLA genotypes and severity of infections extend broadly to several unrelated viruses.

2.4.1 | Relevance to coronavirus

In studies of the *HLA-A*, *HLA-B*, *HLA-DRA* and HLA-*DQA1* alleles among Chinese patients, two *HLA-B*0703 and HLA-DRB1*0301* alleles showed a significant association with SARS-CoV infection.[35] In the Vietnamese population, a case-control study comprising SARS-CoV infected patients, healthy individuals without contact history and staff members who had contact with SARS-CoV infected patients, but had not developed the infection, revealed that *HLA-DRB1*12* showed a significant positive association with developing SARS-CoV.[36] The tendency of patients with the *HLA-DRB1*12* allele to develop infection has been supported in a large study from southern China.[37] The *HLA-DRB4*01010101* allele is another variant in the Chinese population that was found to be significantly associated with genetic susceptibility to infection by

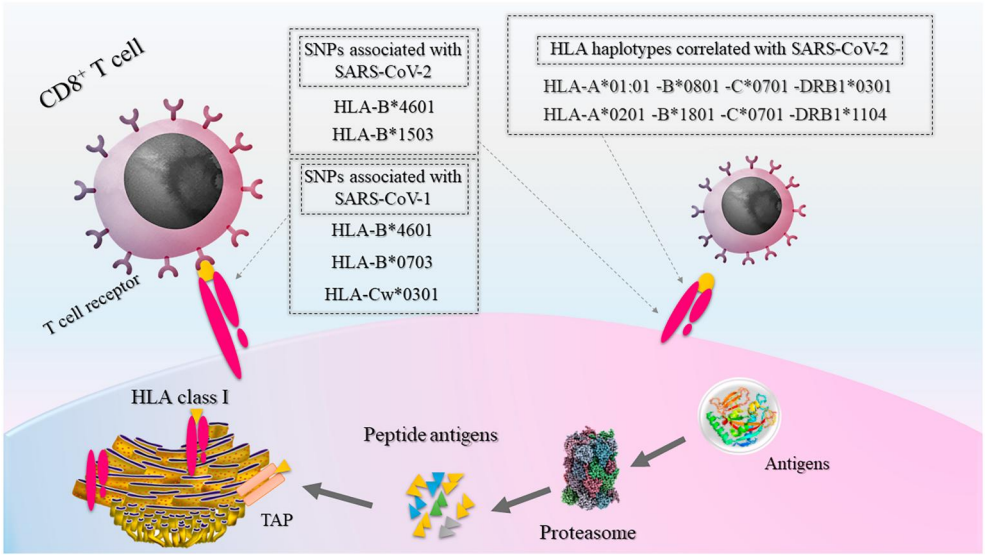

FIGURE 2 Antigen presentation by HLA class I proteins to CD8+ T cells (cytotoxic T cells). Proteins inside the cytosol of cells are degraded by the proteasome into peptide antigens. These peptides further pass through TAP into the ER, and will then bind to HLA proteins. Finally, antigen-bound receptors will translocate through the Golgi apparatus (not shown) to the plasma membrane and present the antigens to cytotoxic T cells. Associations between genetic variants in HLA class I genes with SARS-CoV-1 and -2 are shown in gray boxes. ER, endoplasmic reticulum; HLA, human leukocyte antigen; SARS-CoV, severe acute respiratory syndrome coronavirus; TAP, transporter associated with antigen processing

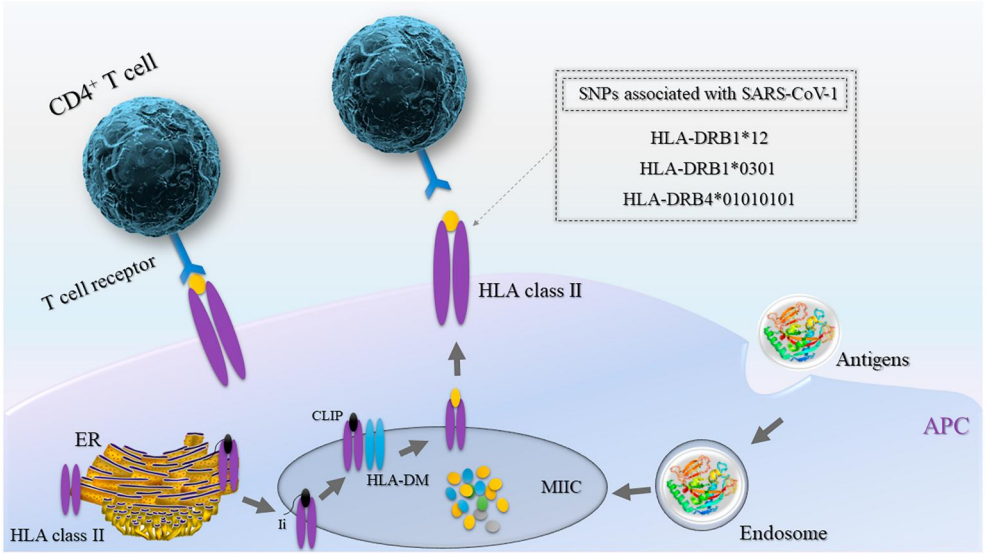

FIGURE 3 Antigen presentation by HLA class II proteins to CD4+ T cells (helper T cells). Extracellular proteins that enter APCs through phagocytosis are then transported into and degraded in MIIC. HLA class II and Ii proteins produced on ribosomes are translocated into the ER to form heterotrimer units. Upon further maturation of trimers in the Golgi apparatus (not shown) and transportation to MIIC, Ii is degraded into CLIP, and HLA-DM induces the replacement of CLIP with peptide antigens within MIIC. Finally, antigen-bound HLAs translocate to the plasma membrane and present the antigens to CD4+ T cells. Associations between genetic variants in HLA class II genes with SARS-CoV-1 are shown in the gray box. APC, antigen-presenting cell; CLIP, class II-associated invariant chain peptide; ER, endoplasmic reticulum; HLA, human leukocyte antigen; Ii, invariant chain; MIIC, MHC class II compartment

SARS-CoV.[38] Furthermore, in Taiwanese association studies, the *HLA-B*4601* and *HLA-Cw*0801* alleles were also found to associate with susceptibility to SARS-CoV infection.[39,40] In studies on SARS-CoV-2, a comprehensive in silico analysis of viral peptide-MHC class I binding affinity across 145 *HLA-A*, *HLA-B* and *HLA-C* genotypes for all SARS-CoV-2 peptides has revealed that the *HLA-B*46:01* allele has the fewest predicted binding peptides for SARS-CoV-2. Conversely, the *HLA-B*15:03* allele shows the greatest capacity to present highly conserved SARS-CoV-2 peptides, suggesting that it could play a protective role through activating T-cell-based immunity.[41]

Another study has uncovered that the two most frequent HLA haplotypes in the Italian population, *HLA-A*:01:01*, *HLA-B*08:01*, *HLA-C*07:01*, *HLA-DRB1*03:01* and *HLA-A*02.01*, *HLA-B*18.01*, *HLA-C*07.01*, *HLA-DRB1*11.04*, show a positive (suggestive of susceptibility factor) and negative (suggestive of protective factor), respectively, significant correlation with both Covid-19 incidence and severity.[42]

2.5 | Fc fragment of immunoglobulin G receptors

2.5.1 | Relevance to coronavirus

Receptors for the constant region of antibodies (FcR) play a crucial role in the regulation of immunity and initiation of local inflammation. The human FCGR2A is composes a crucial link between the humoral branch and the effector cells of the immune system. A functional polymorphism (rs1801274, c.500A>G) in the *FCGR2A* gene, a subclass of immunoglobulin G receptors, shows clinical implications in infectious diseases, either at the level of disease susceptibility or at the level of disease severity.[43]

Genotyping of this SNP in a Chinese study in patients with a moderate course of SARS infection, patients with severe symptoms (ICU admission), patients who died from SARS-CoV infection, and healthy controls demonstrated that ICU patients and deceased subgroups had a significant increase of the GG genotype compared to controls (23% vs. 9%).[44] It is suggested that the GG genotype could be a risk factor for developing a more severe course of SARS-CoV-1 infection, while the AA genotype might show a protective role in the patient outcomes.

2.6 | Complement decay-accelerating factor

2.6.1 | Relevance to influenza virus

Complement decay-accelerating factor (CD55) is a prominent complement-regulatory protein that impedes C5 and C3 convertase activation and thus prevents the activation of C5 and C3 proteins. The rs2564978 SNP in the promoter of *CD55* is associated with severe influenza A(H1N1)pdm09; the rs2564978 TT genotype is associated with remarkably reduced transcriptional activity of the promoter compared to the CC genotype.[45]

3 | INFLAMMATION: A DOUBLE-EDGED SWORD

Inflammation has vital roles in orchestrating innate and adaptive immune responses to pathogens and tissue injury. The production of a variety of proinflammatory cytokines and chemokines induces a counter regulatory anti-inflammatory response to avoid excessive injury. However, sometimes such counter-regulation fails and results in excessive infiltration of inflammatory cells into infected tissues.[2,46]

3.1 | Cytokines

Cytokines are a group of small proteins, including IFNs, interleukins (ILs), chemokines, colony-stimulating factors and tumor necrosis factor-alpha (TNF-α) that are released by specific cells to regulate intercellular signaling (Figure 4). In this section, the elements of inflammation in coronavirus, RSV and influenza infection will be discussed (Table 2).

3.1.1 | IFNs

IFNs are a subgroup of cytokines that have a fundamental role in the immune response against both viral and microbial pathogens.[47] Three major types of IFNs (IFN-I, IFN -II and IFN -III) are characterized based on their receptor specificity.

Relevance to coronavirus

IFN gamma (*IFNG*) is the only member of IFN-II, which is located on chromosome 12. The ability of IFNG to interfere with viral infections through inducing the production of free radicals and other proinflammatory cytokines have made it an intriguing factor to study in determining genetic variants involving both susceptibility and vulnerability to viral infections.

The immunopathological events related to the IFN-mediated pathway have a critical role in the immune response against SARS-CoV infection.[48] In China, a case-control study genotyped the *IFNG* +874 A/T polymorphism (rs2430561) in 476 SARS patients and 449 healthy controls; the *IFNG* c.874A allele was significantly overrepresented in patients compared to the controls. Particularly, the *IFNG* c.874A allele shows a significant association with susceptibility to SARS-CoV infection.[49] This polymorphism has been previously reported to be associated with other infectious diseases such as parvovirus, tuberculosis, and hepatitis B virus infection.[50,51] The T allele of *IFNG* c.874A>T variant prepares a site for binding transcription factor nuclear factor kappa B (NF-κB).[52] It is suggested that the c.874A allele results in the downexpression of *IFNG*, which could impair antiviral responses.

In studies related to Covid-19, a recent investigation uncovered two LOF homozygote variants (p.Trp73Cys, p.Ser422Arg) and one LOF heterozygote variant (p.Pro335del) in the *IFNAR1* gene, as well as one LOF heterozygote variant (p.Glu140fs) in the *IFNAR2* gene in patients with life-threatening Covid-19.[24] IFNAR1 and IFNAR2

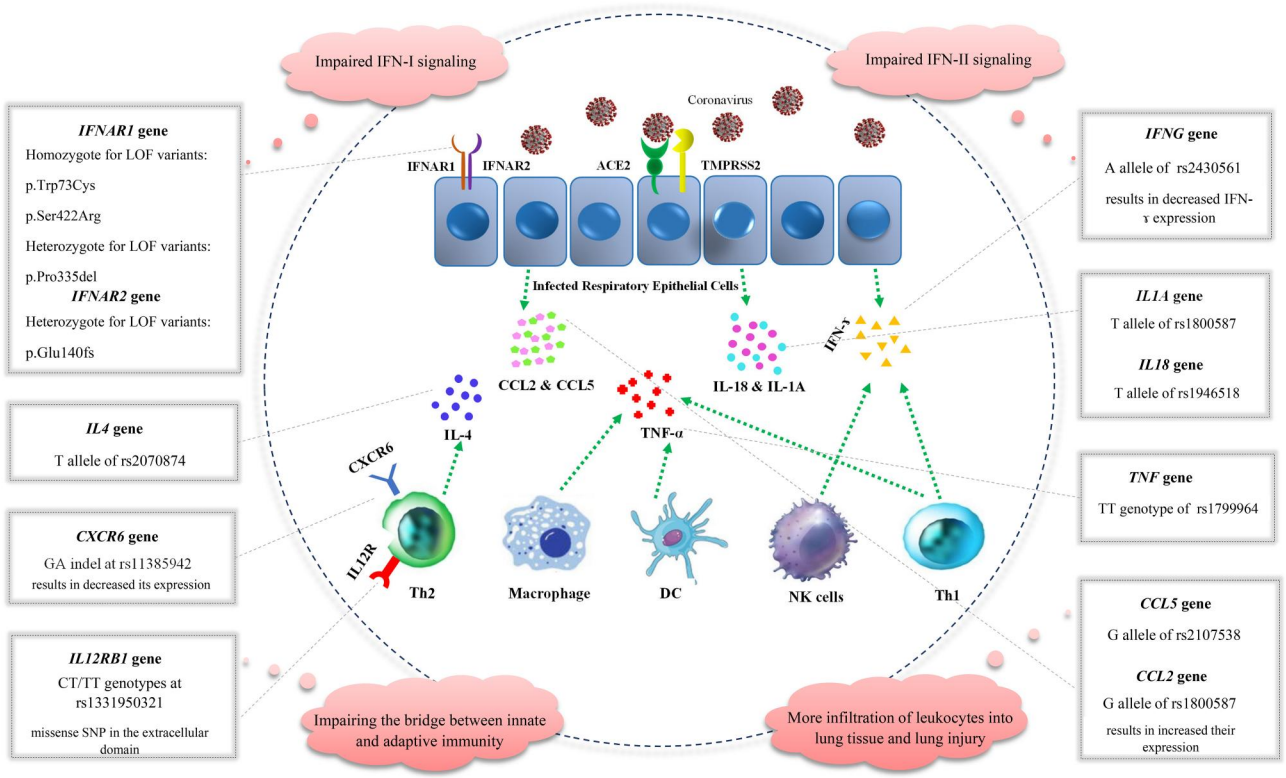

FIGURE 4 Variants in inflammation-related genes underlying the susceptibility to coronavirus. CCL, C-C motif chemokine ligand; DC, dendritic cell; IFN, interferon; IL, interleukin; NK, natural killer cell; Th, T-helper cell

TABLE 2 Summary of studies which reported the inflammation-related genetic variants behind the susceptibility and vulnerability to coronavirus, respiratory syncytial virus and influenza

Gene	Variant	Virus	Country	Allele/genotype effect
Inflammation				
AHSG	rs2248690	SARS-CoV-1	China	AA genotype/protective
CCL2	rs1024611	SARS-CoV-1	China	G allele/risk
CCL5	rs2107538	SARS-CoV-1	China	G allele/risk
	rs2107538	RSV	Brazil	CT genotype/risk
CCR5	rs1799987	RSV	UK	G allele/risk
	rs2734648	RSV	UK	T allele/risk
CX3CR1	rs3732378	RSV	Greece	TT and TC genotypes/risk
CXCR6	rs11385942	SARS-CoV-2	Spain and Italy	Indel of GA/risk
IFITM3	rs12252	Influenza	China	CC genotype/risk
	rs34481144	Influenza	African American	A allele/risk
IFNA5	rs10757212	RSV	Netherlands	T allele/risk
IFNAR1	p.Trp73Cys	SARS-CoV-2	Turkey	CC genotype/risk
	p.Ser422Arg	SARS-CoV-2	Pakistan	CC genotype/risk
	p.Pro335del	SARS-CoV-2	China	Heterozygote for TTC deletion/risk
IFNAR2	p.Glu140fs	SARS-CoV-2	Belgium	Heterozygote for 13-bp deletion/risk
IFNG	rs2430561	SARS-CoV-1	China	A allele/risk
	rs3138557	RSV	China	CA12-/CA12- genotype/risk
IFNL3	rs8099917	Influenza	Iran	TT genotype/risk
IL10	rs1800872	Influenza	Iran	GG and GT genotypes/risk
	rs1800872	Influenza	Mexico	C allele/risk
	rs1800870	Influenza	Mexico	A allele/risk
IL12RB1	rs1331950321	SARS-CoV-1	China	T allele/risk
IL17A	rs2275913	Influenza	Iran	GG and AG genotypes/risk
IL18	rs1946518	SARS-CoV-1	Taiwan	T allele/risk
	rs360721	RSV	Germany	G allele/risk
IL1A	rs17561	Influenza	China	T allele/risk
	rs1800587	SARS-CoV-1	Taiwan	T allele/risk
IL1B	rs16944	Influenza	Iran	AA genotype/protection
	rs1143627	Influenza	China	C allele/risk
IL1RL1	rs1921622	RSV	Netherlands	G allele/risk
IL4	rs2070874	Respiratory infections (RSV, influenza, SARS-CoV-1, and pneumonia)	Meta-analysis of different populations	T allele/Risk
	rs2243250	RSV	Korea	T allele/risk
	rs2243289	RSV	Korea	G allele/risk
	c.8412A	RSV	Korea	A allele/risk
IL4R	rs1801275	RSV	Netherlands	G allele/risk
IL9	rs1799962 & rs2069885	RSV	Netherlands	TT haplotype/risk in girls

TABLE 2 (Continued)

Gene	Variant	Virus	Country	Allele/genotype effect
MX1	rs17000900	SARS-CoV-1	China	A allele/protective
	rs2071430	SARS-CoV-1	China	G allele/risk
OAS1	rs3741981	SARS-CoV-1	Vietnam	G allele/risk
	rs2660	SARS-CoV-1	China	G allele/protective
TNF	rs1799964	SARS-CoV-1	China	CT genotype/protective
	rs1800629	Influenza	Mexico	G allele/risk

subunits comprise the IFN receptor that binds to the type I IFNs including IFN-α and IFN-β.

Relevance to RSV

Members of the IFN type I family are involved in RSV-related infection, as the rs10757212 SNP in *IFNA5* is associated with RSV-related bronchiolitis.[53] Moreover, *IFNA13* rs643070 and *IFNAR2* rs7279064 were associated with RSV-related bronchiolitis in term-born children and *IFNG* rs1861493 was associated with RSV-related bronchiolitis in premature birth.[54]

Another type of genetic variation associated with RSV-related bronchiolitis severity and susceptibility is attributed to the polymorphism in the CA microsatellite (rs3138557) in the first intron of *IFNG*. The number of repeats varies from 11 to 17, and the highest level of IFNG is produced when the number of repeats equals 12 (CA12). Children with the CA12+/CA12+ or CA12+/CA12− genotypes demonstrated a significantly lower RSV bronchiolitis respiratory score compared to those carrying the CA12−/CA12− genotype. Furthermore, the CA12 repeat frequency was lower in RSV-infected children compared to controls; patients in whom CA repeats did not reach 12 had high respiratory scores and severe disease.[55]

Relevance to influenza virus

Several lines of evidence indicate that IFN-III contributes greatly in defense against pathogens that infect respiratory tracts such as influenza A and B virus, which predominantly affect the elderly population. Association of *IFNL3* SNP rs8099917 with influenza virus is controversial as this SNP was associated with influenza virus infection in one Iranian study[56] while no association was observed in another report.[57]

3.1.2 | ILs

ILs are regulatory cytokines involved in the activation and differentiation of immune cells. They could show both pro- and anti-inflammatory functions.

Relevance to coronavirus

IL18 and IL1A are constitutively expressed in the lungs.[58] Investigation of 281 SNPs in the Taiwanese patients with SARS-CoV-1 infection revealed that detectable nasopharyngeal shedding of the virus is associated with the T allele of rs1946518 in the promoter of the *IL18* gene and the T allele of rs1800587 in the *IL1A* gene.[59] It is postulated that these polymorphisms could affect IL gene expression, thereby participating in the clearance of viral infection.

IL12A is another inflammatory cytokine that is naturally produced by macrophages, neutrophils and DCs. A study on cases with SARS-CoV infection and two control groups including healthy individuals without contact history with SARS-CoV-infected patients and 141 healthy individuals with close contacts discovered a significant association between susceptibility to SARS-CoV infection and c.1664 CT/TT genotypes (rs1331950321) in the *IL12RB1* gene.[60] This variant is a missense SNP (p.P534L) in the extracellular coding sequence of IL12RB1 protein.

IL6 is transiently produced in response to infectious agents. Two variants—c.-572C/G (rs1800797) and c.-174G/C (rs1800795)—have been confirmed to affect both the transcription and secretion levels of IL6.[61] Interestingly, the c.-174 G/C variant of the *IL6* gene is significantly associated with the severity of pneumonia.[62] It was demonstrated that carriers of the C allele show a higher IL6 expression and 2.42-fold higher risk for septic shock.[63,64] Moreover, susceptibility to acute lung injury is associated with an *IL6* gene haplotype that spans −1363 to +4835 from the transcription start site.[65,66] It is suggested that *IL6* polymorphisms are involved in the progression of coronavirus infection, and suppression of the IL6 signaling cascade is suggested as a promising therapeutic strategy against severe SARS-CoV-2 infection.[62]

IL4 plays a fundamental role in shaping the immune reaction to pathogens through inducing both T-cell and B-cell differentiation and its dysregulation could interfere with the balance between Th1 and Th2 responses.[67] A meta-analysis of studies on respiratory infectious diseases including RSV, influenza virus, SARS-CoV and pneumonia has revealed that the T allele of rs2070874 polymorphism from the *IL4* gene is significantly associated with the risk of respiratory infections.[68]

Relevance to RSV

Some SNPs in IL genes are believed to be involved in bronchiolitis caused by RSV. In this regard, the *IL1RN* SNPs rs315952 and *IL27* rs181206 are associated with RSV-related bronchiolitis in premature

birth,[54] and the *IL1RL1* SNP rs1921622 is associated with RSV bronchiolitis severity.[69]

Investigation of *IL4*, *IL5* and *IL13* genes in Korean children revealed various SNPs in various regions of these genes, among which the SNPs c.589T (rs2243250), c.-33T (rs2070874), c.8375G (rs2243289) and c.8412A form a haplotype and each was significantly associated with severe RSV infection. However, after statistical correction, the results related to each SNP were marginal.[70]

It is noteworthy that association studies demonstrated different results in different populations; that is, a specific SNP might be significantly associated with a specific disease in one population, but not in another. This is the case for the *IL4* promoter variant rs2243250, which was reported as an RSV-associated variant in Korea[70] while there was no such association observed in Canadian[71] or German cohorts.[72] A similar story holds true for the *IL4R* SNP rs1801275 that was associated with severe RSV in the study of Hoebee et al.,[73] while there was no significant association reported by Marr et al.[71] Similarly, *IL13* SNP 1112C/T (rs1800925) was associated with severe RSV in the study of Puthothu et al.[72] in contrary to the report of Choi et al.[70] The two *IL13* SNPs rs20541 and rs1881457 were investigated for possible association with severe RSV. However, there was no significant association observed.[72]

Other SNPs in ILs that were associated with RSV infection include the *IL18* SNPs 133G/C (rs360721[74]), and *IL6* SNP -174G/C rs1800795, for which the GG and GC genotypes were associated with shorter hospital stay.[75] The *IL10* SNP rs1800872 C allele was also associated with a higher risk of RSV-related wheeze reported by parents at the corrected age of 1.[76] Association of genetic diversity in other IL including *IL19* rs2243191 and rs2243188, *IL20* rs2981573, *IL4R* rs1805015 and *IL7* rs2583762 SNPs, with post-lower respiratory tract infection (LRTI) recurrent wheeze caused by RSV has also been reported.[77]

It is noteworthy that RSV has a gender-specific pattern of infection, as it is more predominant in boys. Investigation of possible genetic factors underlying gender specificity revealed that *IL9* SNP rs2069885 confers disparate effects in boys and girls. The major allele of this SNP in boys was associated with higher susceptibility to severe forms of the disease, but reduced susceptibility in girls. On the other hand, haplotype analysis demonstrated that the TT haplotype was associated with the highest risk of bronchiolitis requiring hospitalization in girls. This haplotype includes the *IL9* SNPs rs1799962 and rs2069885.[78]

Relevance to influenza virus

Variations in *IL1A* and *IL1B* genes are associated with susceptibility to pandemic A/H1N1 influenza virus. Allele T in *IL1A* rs17561 and allele C in *IL1B* rs1143627 are possibly associated with a higher risk of A (H1N1)pdm09 infection.[79]

In the Iranian population, the AA genotype of *IL1B* rs16944 is associated with higher protection against influenza B infection.[57] However, another study stated that the decreased risk of infection is associated with the GG genotype of *IL1B* rs16944.[56] For *IL17A* SNP rs2275913, the lack of allele A is associated with a higher predisposition to Influenza virus.[57]

The rs1554286 SNP in *IL10* is significantly associated with the epiglottitis caused by invasive *H. influenzae* serotype B infection in immunized children. This SNP is in strong LD with two other polymorphisms within the promoter and the recessive genotype of this SNP is associated with epiglottitis.[80]

The *IL10* −1082A (rs1800870) and −592C (rs1800872) alleles were overrepresented in influenza patients and associated with a higher risk of being affected with severe infection. In the case of inflammatory conditions, the *IL10* rs1800870 A allele is associated with lower levels of cytokine production, whereas the *IL10* rs1800870 G allele leads to higher levels of cytokine production. Individuals with the *IL10* rs1800870 AA genotype are more susceptible to severe influenza virus infection.[81] Moreover, the GG and TG genotypes of the *IL10* rs1800872 SNP were associated with severe influenza A/H3N2 disease in the Iranian population[56] while in another study, no association was observed between this *IL10* SNP and severe influenza disease.[57]

3.1.3 | Chemokines

Chemokines are small proteins that belong to the category of cell signaling molecules and induce chemotaxis in nearby cells.[82] Concerning their central roles in inflammatory responses, many chemokines and chemokine receptors have been introduced as potential therapeutic targets for several inflammatory diseases.[83]

Relevance to coronavirus

C-C motif chemokine ligand 5 (CCL5), also known as RANTES, has a fundamental role in the recruitment and migration of T cells toward inflammation sites during acute infections.

Law et al.[84] reported that nonstructural protein 1 (NSP1) of SARS coronavirus can strongly induce CCL5 expression in human lung epithelial cells. Regarding the SARS-CoV epidemic in China, it was found that the G allele of *CCL5* c.-28C/G polymorphism (rs2280788) was significantly associated with more severe symptoms and admission to ICU or deaths.[85] This SNP could be involved in regulating *CCL5* expression by modifying the binding site of the NF-κB transcription factor.[86]

CCL2 is involved in the chemoattraction of monocytes and polarization of T-helper cells. CCL2 is one of the upregulated chemokines in monocytes and lung epithelial cells during the early stage of SARS-CoV infection.[87] It has been revealed that the higher plasma levels of CCL2 in patients with SARS-CoV-1 infection is significantly correlated with severe symptoms.[88] A functional SNP (rs1024611G/A) is located in *CCL2* promoter that affects the expression level. The G allele triggers higher expression of *CCL2* and is associated with more infiltration of leukocytes into tissues compared to the A

allele.[89] It has been suggested that the rs1024611 variant could be involved in interindividual differences of host vulnerability to SARS-CoV infection.[90]

A genome-wide association study on patients with severe Covid-19 (defined as respiratory failure) and control participants from Italy and Spain has been recently conducted.[91] This investigation has uncovered two association signals on chromosome 3p21.31 and 9q34.2 which cover a cluster of six genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6* and *XCR1*) and the ABO blood group, respectively. Accordingly, the rs11385942 insertion–deletion GA or G variant at 3p21.31 locus is associated with Covid-19-induced respiratory failure with genome-wide significance. Interestingly, the locus contains genes encoding chemokine receptors, including *CCR9* and *CXCR6*. The risk allele GA is associated with lower expression of *CXCR6* and higher expression of *SLC6A20*, and *LZTFL1* in human lung cells. CXCR6 regulates the location of lung-resident memory CD8+ T cells during the immune reaction to airway pathogens. It should be noted that further studies will be needed to reveal the functional consequences of detected associations.

Relevance to RSV

The *CCL5* SNP rs2107538 is associated with RSV and RSV subtype A-associated bronchiolitis.[33] Polymorphisms located within the promoter (−408G/A rs2107538; −28G/C rs2280788) and the first intron (In1.1T/C rs2280789) of *CCL5* are in strong LD and it was demonstrated that a common combined genotype of these polymorphisms is associated with severe RSV infection.[92]

In the category of chemokines, the *CX3CR1* SNP rs3732378 (p.T280M; c.935C/T) variant was associated with RSV-related bronchiolitis, which is due to an interruption in the affinity of CX3CR1 to its ligand fractalkine. Carriers of the 280M allele were more prevalent among patients and individuals with genotypes containing this allele were more likely to be hospitalized due to RSV-related bronchiolitis.[93]

CCR5 is the receptor of CCL5 and CCL3 that recruit various immune cells such as monocytes, T cells and basophils, and so on. Regarding RSV infection, the −2459G (rs1799987) and −2554T (rs2734648) variants of *CCR5* are associated with severe RSV-related bronchiolitis.[94] The effect of rs2734648 is not functionally clear, and the impact of rs1799987 is debating as it leads to both increased and decreased expression of *CCR5*.[75]

Chemokine (C-X-C motif) ligand 9 (CXCL9)/induced by gamma IFN is a small cytokine of CXC chemokine and participates in several cellular and immune-related processes.[95] There is a significant association between *CXCL9* rs2276886 and post-RSV LRTI recurrent wheeze.[77]

3.1.4 | TNF

TNF is vital for the innate immune response against pathogens and is a key mediator of inflammatory response. Dysregulation of this cytokine could lead to tissue injuries through the inflammation cascade and therefore, its gene regulation is a considerable factor in the pathobiology of inflammation.[96]

Relevance to coronavirus

A case-control study in China including 75 SARS patients, 41 healthcare workers, and 92 healthy controls revealed that the CT genotype compared to the TT genotype at the c.-204 locus of *TNF* gene (rs1799964) could be a protective factor for SARS-CoV infection.[97]

Relevance to RSV

TNF receptor superfamily member 1B (TNFRSF1B) is a TNF-binding receptor that mediates the effects of TNF in autoimmunity, inflammation and tumorigenesis.[98] In patients affected with RSV, *TNFRSF1B* rs1061622 was associated with post-RSV LRTI recurrent wheeze.[77]

Relevance to influenza virus

The *TNF* SNP c.-308G rs1800629 was overrepresented in patients affected with influenza and was associated with disease severity.[81]

3.2 | Other inflammation-related genes

3.2.1 | IFN-inducible genes: Inhibitors of viral replication or viral entry

Relevance to coronavirus

IFN-induced GTP-binding protein Mx1 (MX1) is an antiviral protein that prevents viral replication. A large case-control study in China, the A allele of the *MX1* c.-123C/A variant (rs17000900) is significantly associated with a lower risk of SARS coronavirus infection.[99] Moreover, the G-allele of c.-88G/T polymorphism (rs2071430) was found more frequently in the hypoxemic group compared to the nonhypoxemic group of SARS-CoV infected patients.[100] Interestingly, the G allele induces lower promoter activity rather than the T allele.[101]

Another IFN-inducible gene is the *OAS1*, which is a member of the 2′-5′ oligoadenylate synthetase family. A study on Vietnamese SARS-CoV-1 patients and controls revealed that the G allele of nonsynonymous A/G SNP in exon 3 of the *OAS1* gene (rs3741981) affects disease susceptibility and progression of SARS.[100] In China, genotyping of SARS-CoV cases and close-contact uninfected controls for the *OAS1* gene indicated that the G allele of rs2660 polymorphism in the 3′-untranslated region is associated with a protective effect on SARS infection.[102]

Relevance to influenza virus

IFN induced transmembrane proteins (IFITMs) are located within the endolysosomal and plasma membranes to disrupt membrane fusion between the host cell and viruses, and confront viral entry. SNP rs12252 and rs34481144 in the promoter of *IFITM3* are associated with severe influenza virus including.[103] Although some studies declared an association between rs12252C as a risk allele with

severe influenza A virus, other studies suggest that homozygosity for this allele might predispose individuals to a mild form of influenza but not the severe form,[104] or suggest that this allele was not associated with pediatric influenza virus infection.[105] This SNP was not associated with seasonal influenza-related hospitalization.[106]

On the other hand, allele C of the *IFITM3* SNP rs12252 leads to a change of splice site sequence and was significantly overrepresented in hospitalized patients. Moreover, the minor *IFITM3* CC genotype was linked to decreased restriction of influenza virus in vitro. In conclusion, IFITM3 is an important factor in morbidity and mortality of influenza virus infection.[107]

4 | PRIMARY IMMUNODEFICIENCY AND COVID-19

Primary immunodeficiency (PID) patients are characterized by an impaired immune function that could result in susceptibility to severe infections. It is suggested that the frequency of severe Covid-19 is significantly higher in these patients. However, an opposite possibility is that PID patients are protected from Covid-19 due to suppression of cytokine storm, which is caused by a deficient inflammatory response in these patients.[108] Therefore, regarding the two mentioned scenarios in the introduction, PID could affect individuals' susceptibility to Covid-19. Similar to general populations, PID patients with Covid-19 demonstrate variable disease severity and outcome depending on the type of immune deficiency.[109–112] Patients with a mutation in antiviral immunity-related genes are severely affected with Covid-19. Studies have reported that mutations in *STK4*, *RAB27A*, *IL1RN*, *IFNAR2*, *IRF7* and *TLRs* genes were associated with Covid-19 severity in PID patients.[24,113–116]

In contrast, patients with inflammatory pathway dysfunction show milder Covid-19 manifestations.[108] A recent investigation on two agammaglobulinemia and five common variable immune deficiency (CVID) patients revealed that the agammaglobulinemia patients showed mild Covid-19 symptoms. In contrast, CVID patients manifested a severe form of Covid-19 and required ICU admission.[117] It is suggested that the absence of B cells in agammaglobulinemia patients results in suppressed development of inflammatory cascade and cytokine storm. Similarly, two agammaglobulinemia patients with Bruton's tyrosine kinase (*BTK*) germline mutation (S578Y) recovered from Covid-19 without intensive care.[118]

Collectively, a recent systematic review and meta-analysis reported that PID patients have a 1.55-fold higher risk of manifesting severe Covid-19, but this observation is statistically nonsignificant.[119]

5 | CONCLUSION

The attention given to the roles of interindividual immunogenic variants in infectious diseases has become more remarkable over the past decade. The results of host immunogenetic-focused studies suggest that the genetic background of the host could affect the levels of proinflammatory and anti-inflammatory cytokines and might modulate the progression of Covid-19 in affected patients. This review provides promising clues related to the potential benefits of using immunotherapy and immune modulation for respiratory infectious disease treatment in a personalized manner. Moreover, these results provide insights for risk assessment and subsequent preventive interventions. Employment of high throughput sequencing and powerful bioinformatics methods, now broadly available, could further help verify the involved genetic variants in different ethnic groups and are expected to continuously contribute to the genetic basis of Covid-19 susceptibility.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

AUTHOR CONTRIBUTIONS

Farzaneh Darbeheshti and Mojdeh Mahdiannasser equally carried out the literature review, visualization, and writing-original draft. Bruce D. Uhal, Shuji Ogino and Sudhir Gupta critically revised the work. Nima Rezaei contributed to the conceptualization, project administration, investigation and validation. All authors contributed to the article and approved the submitted version.

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