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REVIEW

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Individual genetic variability mainly of Proinflammatory cytokines, cytokine receptors, and toll-like receptors dictates pathophysiology of COVID-19 disease

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Abstract

Innate and acquired immunity responses are crucial for viral infection elimination. However, genetic variations in coding genes may exacerbate the inflammation or initiate devastating cytokine storms which poses severe respiratory conditions in coronavirus disease-19 (COVID-19). Host genetic variations in particular those related to the immune responses determine the patients' susceptibility and COVID-19 severity and pathophysiology. Gene polymorphisms such as single nucleotide polymorphisms (SNPs) of interferons, *TNF*, *IL1*, *IL4*, *IL6*, *IL7*, *IL10*, and *IL17* predispose patients to the severe form of COVID-19 or severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). These variations mainly alter the gene expression and cause a severe response by B cells, T cells, monocytes, neutrophils, and natural killer cells participating in a cytokine storm. Moreover, cytokines and chemokines SNPs are associated with the severity of COVID-19 and clinical outcomes depending on the corresponding effect. Additionally, genetic variations in genes encoding toll-like receptors (TLRs) mainly *TLR3*, *TLR7*, and *TLR9* have been related to the COVID-19 severe respiratory symptoms. The specific relation of these mutations with the novel variants of concern (VOCs) infection remains to be elucidated. Genetic variations mainly within genes encoding proinflammatory cytokines, cytokine receptors, and TLRs predispose patients to COVID-19 disease severity. Understanding host immune gene variations associated with the SARS-COV-2 infection opens insights to control the pathophysiology of emerging viral infections.

KEYWORDS

coronavirus disease-19, cytokines, genetic variations, immunity, toll-like receptors

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1 | INTRODUCTION

In December 2019, the first outbreak of a pneumonia-like disease with unknown etiology was reported in Wuhan, China.[1] Chinese authorities primary recognition announced that the pathogen responsible for this disease was a novel coronavirus (2019-nCoV) or COVID-19.[2] This coronavirus was called "severe acute respiratory syndrome coronavirus-2" (SARS-CoV-2) by the World Health Organization.[2,3] COVID-19 is associated with several clinical signs among patients, mostly such as fever, cough, and fatigue, followed by rare cases of congestion, rhinorrhea, sore throat, and diarrhea.[4–6] Those 2019-nCoV infection clinical features common with the SARS-COV-1 and Middle East Respiratory Syndrome (MERS) have included fever, dry cough, dyspnea, and bilateral ground-glass opacities by chest computerized tomography (CT) scans. Moreover, COVID-19 causes immune dysfunction, acute respiratory distress syndrome (ARDS) as well as multiorgan failure. Among patients suffering from severe COVID-19, ARDS is the most common and destructive form of the disease.[6,7] ARDS is developed by a series of mechanisms including the abnormal activity of the renin-angiotensin apparatus, cytokine storm, neutrophil stimulation, vitamin D receptor (*vdr*) gene expression, oxidative stress, and enhanced coagulopathies.[8–11] The most frequently reported laboratory abnormalities included increased levels of C-reactive protein (CRP) and lactate dehydrogenase (LDH) and reduced lymphocyte count.[12] Cytokine storm and various genetic variations/polymorphisms in the host defense system predispose to a severe SARS-COV-2 disease via affecting the level of the encoded protein.[13,14] Genetic variations in the host body such as immune-related genes and also the SARS-COV-2 variants determine the clinical outcome of the disease. Therefore, in this study, those genetic variations mostly of encoding genes associated with the immune responses to the COVID-19 disease predisposition or individual vulnerability were reviewed during 2019-2022.

2 | SARS-COV-2 PATHOPHYSIOLOGY AND RISK FACTORS

Following the binding (via viral spike/S, small envelope glycoprotein/E, and membrane/M) and penetration of the SARS-COV-2 into the respiratory epithelial cells via binding to the angiotensin-converting enzyme-2 (ACE2) receptors mostly by viral spike protein, some proinflammatory cytokines are secreted[15,16] (Figures 1 and 2). These cytokines include interferons, granulocyte colony-stimulating factor (G-CSF, filgrastim), monocyte chemoattractant protein 1 (MCP-1), interleukin 1 B (IL1B), endothelial growth factor (EGF), IL6, IFNγ, IP10, macrophage inflammatory protein A (MIP-1α or MIP1A), tumor necrosis factor (TNF)-α, IL8, IL4, and IL10, and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.).[17–19] Higher levels of IL2, IL6, IL7, IL10, IP10, MCP-1, IL17A, TNF-α, MIP1A, and GCSF have

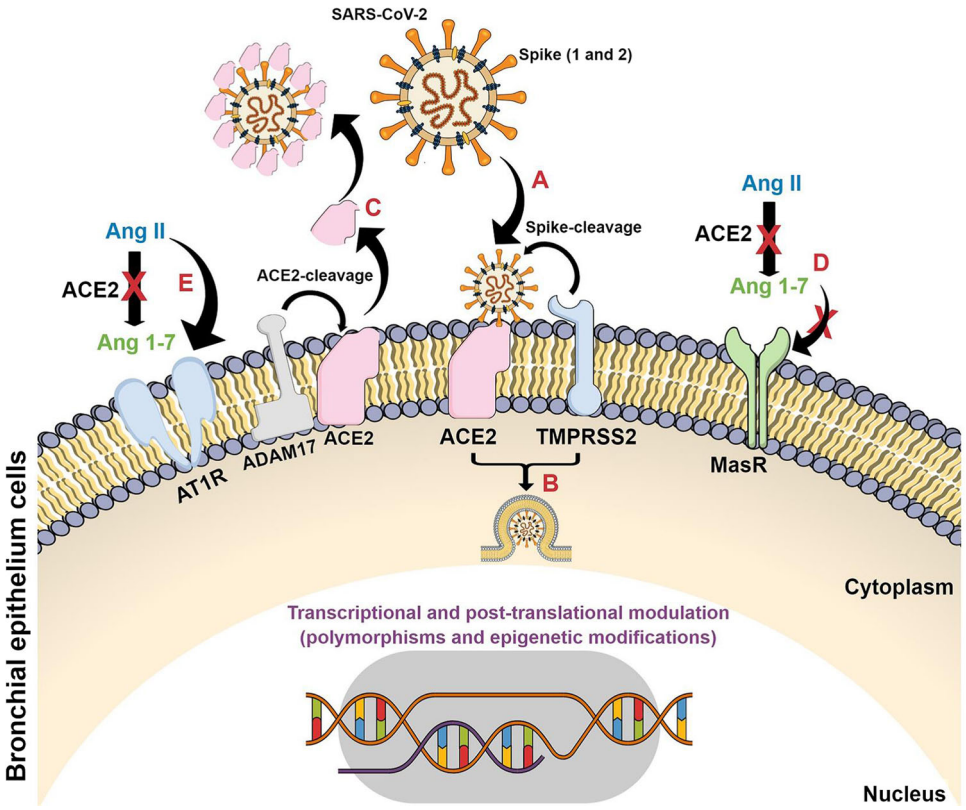

FIGURE 1 Mechanisms of SARS-COV-2 binding to the ACE2 receptor and cell penetration. ACE2, angiotensin-converting enzyme-2; SARS-COV-2, severe acute respiratory syndrome coronavirus-2; TMPRSS2, transmembrane protease serine-type 2.

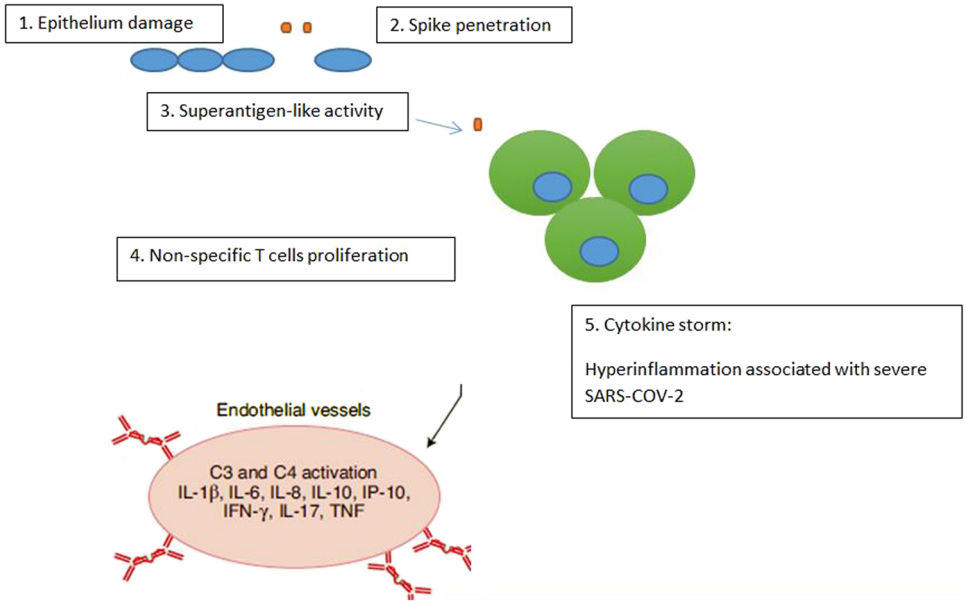

FIGURE 2 The mechanism of cytokine storm induction in SARS-COV-2 pathophysiology. SARS-COV-2, severe acute respiratory syndrome coronavirus-2.

been determined among those patients with severe SARS-COV-2 or cytokine storm and also T cell lymphopenia compared to those with mild or moderate infection.[20,21] High IL6 serum levels have been associated with some conditions such as pneumonia (early death, plus TNF-α), asthma, atopic dermatitis, and COVID-19 severity. Noticeably, polymorphisms in cytokines result in their serum variations which alter (positive or negative) proinflammatory responses to SARS-COV-2.

Male gender, older ages (>65 years), underlying medical conditions (diabetes, cancer, hypertension, chronic respiratory, and cardiovascular disorders), and chronic obstructive pulmonary disease (COPD) include major risk factors. Other significant factors include overweight, tobacco exposure, high LDH and International normalized ratio, low SPO_2, serum albumin, public education/community knowledge and behaviors, antiviral use policies, individual/familial/population genetics, racial factors (non-Hispanic Blacks), and lymphopenia <900/mm^3.[22–27] The gender differences in responses to SARS-COV-2 attribute to the important role of X-linked genes participating in immune stimulation. Lower socioeconomic conditions have also played a significant role in the COVID-19 vulnerability.[28]

3 | HUMAN GENETIC VARIATIONS AND COVID-19 SEVERITY

Human genetic variations have been demonstrated to associate with COVID-19 severity. Genome wide association studies have demonstrated major genetic mutations including *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*,[29,30] *ABO* (rs657152, rs9411378, and rs912805253), *INFAR2* (rs2236757 and rs13050728), Oligoadenylate synthetases (*OAS1* and *OAS3*), dipeptidyl peptidase 4 (*DPP4*/CD26) rs13015258,[29,30] *DPP9*, intercellular adhesin molecules (*ICAM5*), tyrosine kinase 2 (*TYK2*), human leukocyte antigens (*HLA-G*, *HLA-DPB1*), coiled-coil α-helical rod protein 1 (*CCHCR1*), *ACE2*, Mucin 5B (*MUC5B*), and Forkhead box P4 (*FOXP4*).[29–34] Moreover, this association has been deciphered regarding single nucleotide polymorphisms (SNPs) in the interferons, *IL1*, *TNF*, toll-like receptors (TLRs), *IL6*, *IL10*, *IL17* genes, and those encoding transmembrane protease serine-type 2 (*TMPRSS2*), glucose-regulated protein 78 kDa (*GRP78*), *ERAP2*, *Adam17*, *APOE*, and *PCSK3*, cluster of differentiation 147 (CD147), 2′-5′-Oligoadenylate synthases (*Oas*) (p.Arg47Gln, p.Ile99Val, and p.Arg130His), *HLA-B*46:01/A25:01/C01:02*, *CCR9*, *CXCR6*, *SLC6A20*, and CRP (rs1205) which predispose SARS-COV-2 infection.[35–40] Similar relations were unraveled regarding variations in genes encoding UNC13D and AP3B1 germline associated proteins to the SARS-COV-2 infection.[41] The post-COVID-19 pulmonary fibrosis has also been associated with some genetic mutations such as in *MUC5B* and *TERT* genes. Genetic mutations in chromosomes 5q32 and 12q22 loci have been associated with COVID-19 severity.[42] SNPs have caused serum variations in related encoded proteins which substantially alter immune responses in exposure to SARS-COV-2 and dictate the outcome of the disease. In addition, it was recently unraveled that the *SERPINE1* rs6092 variant was associated with impaired coagulation among SARS-COV-2 infected patients.[43]

4 | INTERFERONS POLYMORPHISMS

Interferons responses impairments diminish the antiviral capacity. An SNP within the interferon-induced transmembrane protein 3 (*IFITM3*) gene (rs12252-C/C) has been associated with influenza and COVID-19 severity.[44–47] This variant has been also associated with intensive care unit (ICU) admission. *IFNAR1* (p.Trp73Cys, p.Ser422Arg, and p.Pro335del)

and *IFNAR2* (p.Glu140fs) and rs2236757—A/G variants have been associated with increased levels of SARS-COV-2. The *IFN-β* (rs2071430—G/T) and *INF-γ* SNPs in African and Asian populations have been related to the infection of both SARS COV and COVID-19.[30,48] Moreover, *IFN-γ* + 874A/T (rs2430561) and A/C polymorphisms were associated with severe SARS COV in Chinese population.[49] Additionally, some loss of function variants of interferons (*TBK1*, *IFIH1*, *IRF3*, *IRF7*, and also *TLR3*) have been associated with severe disease.[48,50]

5 | *TNF* GENE POLYMORPHISMS

TNF-α has an important role in the acute phase of inflammation and chronic degenerative diseases.[51] TNF-α levels increase during respiratory viral infections and the encoding gene SNPs association with SARS COV was shown by Wang et al.[52] However, *TNF* rs1800629, causing TNF-α serum level enhancement and higher reaction to inflammation, has played a protective role against pediatrics sepsis, while *TNF*-863C/A (rs1800630) has increased the risk. Therefore, these mutations are age-dependent. Furthermore, the *TNF* rs909253 allele has been significantly more common in COVID-19 patients than in the control population.[53] In a recent study, TNFRSF1B rs3397 or TT genotype was associated with lower Horowitz index (PaO_2/FiO_2 ratio) compared to CT + CC genotypes being related to different TNFR1 and TNFR2 levels.[54]

6 | INTERLEUKINS POLYMORPHISMS

IL1 RN (rs315952—T/C) and *IL4* (rs2070874—C/T/*IL4* + 1059 C/T) SNPs have been associated with COVID-19 severity.[55,56] The SNPs in the *IL6* gene have been associated with pneumonia and COPD and also certain viral infections such as hepatitis B virus, hepatitis C virus (HCV), and influenza virus.[57–59] Low rate of *IL6* CC (rs1800795) SNP was related to the persistence of HCV infection.[57] A study revealed that *IL6* rs1800795 G allele protected against pneumonia-induced sepsis, but *IL10* rs1800896 A allele enhanced the risk of the disease.[60] Moreover, 7p15.3 (*IL6*–174C allele) has been related to the severity of pneumonia and COVID-19. IL6 also affects the $CD4^+$ T cells' fate and causes the COVID-19 severity.[61–63] In addition, *IL6*, *IL10*, and *IL12B* SNPs have been associated with daily death rates mainly due to hypertension, cardiovascular diseases, obesity, and asthma.[64–67] In a study, among severely ill COVID-19 patients ($n = 100$), *the IL6* gene was significantly expressed higher compared to that in the control population ($n = 324$) which was correlated to the higher mortality rate. They determined that *IL6* rs1800795 and rs2228145 SNPs were associated with severe forms of the COVID-19.[68] Moreover, *IL6* rs1800797 and rs1800795 SNPs have been related to alterations in serum levels and exacerbation of various diseases.[69–71]

Furthermore, *IL10* rs1518110 SNP has been related to its overexpression and disease severity.[72] However, in some studies, the *IL10* SNPs have not been associated with the SARS COV.[49,73–75]

In addition, the significant association of *IL-17A* AG (rs2275913), *IL17F* TT (rs763780), and *IL10* AG (rs1800896) SNPs with international severity and death outcome due to the COVID-19 has been deciphered.[73] Noticeably, *IL10* rs1800871 and rs1800872 genotypes among 193 COVID-19 patients, were not significantly associated with the disease severity[76] (Table 1). *IL17* gene polymorphisms have been associated with ARDS, SARS COV, MERS, and SARS-COV-2 in which the decrease in the IL17 levels was protective, but increased levels were related to the disease severity. It has been exhibited that enhanced circulating and alveolar levels of IL17A have been associated with neutrophil recruitment, alveolar permeability, and organ dysfunction in ARDS.[77] A hypothetic paper proposed the role of IL17 in the stimulation of proinflammatory responses and cytokine

TABLE 1 Major genetic variations (SNPs) in the immune-related genes, mainly of cytokines associated with the susceptibility to the COVID-19.

Gene	Genotype	Effects
TMPRSS2	rs2070788, rs9974589, rs7364083	SARS-COV-2 infection
TNF promoter	rs1800630	Higher reaction to inflammation
IL1A	rs1946518	COVID-19 severity
IL10	rs1800872, rs1800896, rs8178562	Overexpression, enhanced death outcome
IL6	rs1800795, rs2228145	Increased serum level, disease severity
IL17A	rs2275913	International severity and death outcome
IL17F	rs763780	
IFN-β	rs2071430	SARS and COVID-19 severity
IFNAR2	rs2236757	COVID-19 severity
CXCR2	rs1126579	COVID-19 severity
TNFRSF1B	rs1061624, rs3397	COVID-19 severity
IFITM3	rs12252	SARS-COV-2 severity
CD26/DPP4	rs13015258	SARS-COV-2 infection
DBP	rs7041	COVID-19 prevalence and mortality
TLR3	rs3775290	SARS-COV-2 infection
TLR7	rs179008	Low expression, SARS-COV-2 infection
TLR4	rs4986790, rs4986791	Higher serum levels of IL6, SARS-COV-2 infection

Abbreviations: CXCR2, CXC chemokine receptor-2; IFITM3, interferon-induced transmembrane protein 3; SARS-COV-2, severe acute respiratory syndrome coronavirus-2; SNPs, single nucleotide polymorphisms; TLR, toll-like receptor; TMPRSS2, transmembrane protease serine-type 2; TNFRSF1B, tumor necrosis factor receptor 2.

storm in COVID-19 and also proposed to target IL17 as a therapeutic route for improving the symptoms.[78]

7 | CHEMOKINES POLYMORPHISMS

Chromosome 3 (3p21) loci variations have been suggested to play a role in COVID-19 severity.[29] Some putative coreceptors genes (*LZTFL1*, *SCL6A20*, and *FYCO1*) and chemokines and their receptors have been mentioned such as *XCR1*, *CCR6*, and *CCR9*. Moreover, flanking genes (*CCR1*, *CCR2*, and *CCR3*) are also considerable.[79] It has been unraveled that *CXCR6* and *CCR9* chemokine receptor genes play an important role in the COVID-19 protection in lung and whole blood, respectively.[80]

8 | CYTOKINES RECEPTORS POLYMORPHISMS

It was primarily found that various cytokines and VEGF have higher serum levels in COVID-19 patients compared to healthy subjects, suggesting that cytokines and their receptors play a role in the disease development.[81–83] A bioinformatics anticipation study using cloud-based software tools demonstrated that *VEGF* Q472H (rs1870377) *CXCR2* rs1126579, *TNFRSF1B* rs1061624, and *IL10RB* rs8178562 receptors SNPs were possibly related to severe COVID-19. The three latter SNPs cleave the mRNAs−miRNA binding sites.[83]

9 | TLRs GENES POLYMORPHISMS

TLRs recognize pathogen-associated molecular patterns and response to pathogens through elicit of acquired immunity such as proinflammatory cytokines release (TNF-α, IL1 β, and IL6 by TLR3 and IFN-α, IFN-β, and IFN-λ by TLR7).[84,85] *TLR3* gene expression has regulated the influenza A virus and rhinovirus infection.[86–88] *TLR3* rs3775290 heterozygous genotype "C/T" has been associated with the HCV infection.[89] Additionally, *the TLR7* rs179008 genotype has exacerbated bronchial asthma.[90] More relevantly, the elimination of SARS-COV-2 has been facilitated by TLRs2-9 (mostly TLRs 3 and 7) pool.[91–93] Mice deficient in some TLRs encoding genes such as *TLR3*, and allelic variation (Ticam2) and *TLR7* have exhibited higher SARS-COV-2 infection. The intron variant in the *IFNAR2* gene (rs2236757) and Interferon-inducible transmembrane (*IFITM*) genes such as *IFITM3* rs12252 genotype has been associated with SARS-COV-2 infection.[94] It was demonstrated that the *TLR3* rs3775290 and *TLR7* rs179008 genotypes were significantly associated with increased risk of COVID-19 pneumonia but not the disease outcome.[95] They also found that males with *TLR3* SNP (T/T polymorphism) were more susceptible to the disease. *TLR7* rs179008 genotype has been also associated with lower expression levels and additionally, HCV and

TABLE 2 Novel mutations in the SARS-COV-2 genome.

Gene	Motif variation	SARS-COV-2 variant
ORF1a	Δ106-108, L438P, T85I	B.1.526
	T100I, A1708D, 12230T, Δ3675-3677	B.1.1.7
	T265I, K1655N, K3533R, Δ3675-3677	B.1.351
	S1188C, A1795Q, Δ3675-3677	P.1
ORF1b	Q88H, P323L	B.1.526
	P314L	B.1.1.7
	P314L	B.1.351
	P314L	P.1
	P323L	B.1.36
	D1183Y	B.1.427/429
	E1264D	P.1
Accessory protein 3a	Q57H	B.1.526
	Q57H	B.1.351
	S253P	P.1
Accessory protein 8	Q27, R52I, Y73C	B.1.1.7
	E92K	P.1
Nucleocapsid protein	D3L, G204R, S235F, T205I	B.1.1.7
	R203K, G204R, P80R	P.1
	A12G	B.1.525
	P199L, M234I	B.1.526
Envelope protein	L21F	B.1.525
	P71L	B.1.351
Membrane protein	C64F	B.1.525
	I82T	B.1.36
Spike protein	L18F, T20N, P26S, Δ69-70, D138Y, Δ144, R190S, Δ242-244, K417N/T, N440K, E484K/Q, N501Y, D614G/R, H655Y, T1027I, V1176F	P.1 B.1.526 B.1.427/429 B.1.617 B.1.525 B.1.351 B.1.298
	L5F, T95I, D253G, D614G/R, A701V	
	S13I. R21T, W152C, E154Q, Q218H, E484K/Q, L452R, D614G/R, P681R	
	H1101Q, P681R	
	Q52R, A67V, Y453F, D614G/R, Q677H, F888L	
	B80A, D215G, R246I, K417N/T, F484K/Q, N501Y, D614G/R	
	M1229I, I692V, Y453F	

Abbreviation: SARS-COV-2, severe acute respiratory syndrome coronavirus-2.

HIV infection with alteration in responses. Another study in Egypt, demonstrated that among 300 adult patients with COVID-19, *TLR4* gene (Asp299Gly or rs4986790, and Thr399Ile or rs4986791) SNPs were significantly higher among patients correlating with higher serum levels of IL6.[96] A study among 150 middle-aged COVID-19 patients and 135 healthy volunteers exhibited that TLR7 (rs3853839) GG genotype was significantly more frequent in COVID-19 patients compared to control population (38.7% vs. 4.4%). Additionally, *TLR7* mRNA expression levels were significantly higher among patients, particularly among those with GG genotype (rs3853839). Moreover, significantly lower WBC but higher IL6, CRP, and ferritin levels were observed among patients.[97] Therefore, these SNPs were correlated with SARS-COV-2 infection, cytokine storm, and patients' higher mortality rates. In addition, *TLR9* rs352162, rs352162, and rs187084 SNPs were associated with HCV infection and ICU admission. It was hypothesized that TLR-9 may also participate in the combat against COVID-19. Owing to the high rate of CpG-Motifs in the SARS viral sequence, TLR9 controversially participates in lung complications.[98] Hence, the use of TLR9 antagonists in combination with the Remdesivir possibly contributes to COVID-19 disease improvement.

10 | SARS-COV-2 VARIANTS AND IMMUNE ESCAPE

Our aim in this section was to uncover the association of host genetics and SARS-COV-2 variants such as VOCs, however, to the best of our knowledge, there is no published data in this regard. There has been cross-reactivity between various vaccines and COVID-19 variants related to immune responses.[99–101] These data points supposedly elicit similar immune responses by genotype variants of COVID-19. Delta variant (60% more transmissible than alpha variant) has shown resistance to some monoclonal antibodies such as bamlanivimab. Additionally, sera from convalescent individuals were fourfold less reactive against the Delta variant.[102,103] However, this study did not provide any evidence of host immune gene mutations. A variation in the receptor-binding β-loop-β motif of Delta variant (B.1.617.2) spike protein was associated with lower avidity to neutralizing antibodies.[104] Furthermore, mutations in the Omicron variant such as spike protein have an outstanding effect on the immune escape.[105] Novel mutations in the SARS-COV-2 genome have been depicted in Table 2.[106–108] Hence, particular relation between host immune gene variations and the infection of SARS-COV-2 VOCs is warranted in future studies.

11 | CONCLUSION

Host genetic variations in particular those related to the immune responses determine the patients' susceptibility and COVID-19 disease and related pathophysiology. Immune gene polymorphisms such as in interferons, *IL1*, *IL4*, *IL6*, *IL7*, *IL10*, and *IL17* genes predispose patients to develop severe COVID-19. Various cytokine and chemokine polymorphisms and receptors are associated with the outcome of COVID-19 depending on the effect of occurring variation. *TNF* gene SNPs has been associated with higher/intense inflammatory responses. Genetic variations in *TLR3*, *TLR4*, *TLR7*, and *TLR9* genes have been related to the COVID-19 severe respiratory symptoms. However, the specific association of SARS-COV-2 VOCs and host genetic mutations in the disease severity remains to be uncovered. Prescription of cytokine storm inhibitors such as corticosteroids, cyclosporine, and etoposide to regulate the T cells responses can be helpful.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author upon reasonable request.

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