Review

The Role of MHC System in COVID-19 Susceptibility: A Qualitative Review of Current Literature

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Coronavirus disease-2019 (COVID-19) is a novel pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). It presents with wide variations in disease severity, and certain populations appear to be more susceptible than others. The mechanisms of such heterogeneity in disease presentation and susceptibility are largely unclear, and this review article aims to examine the existing evidence for the involvement of the human Major Histocompatibility Complex (MHC) system, which is also known as the Human Leukocyte Antigen (HLA) system, as potential effectors of such heterogeneity. We critically examined peer-reviewed case-control, cohort, and in-silico studies, and classified HLA class 1 and 2 alleles into risk and protective alleles based on existing evidence. Furthermore, we summarized the relationship between HLA-DR expression and COVID-19 pathophysiology based on functional studies. We postulate that the identification of HLA alleles that confer risk or protection for COVID19 will not only shed light on understanding disease epidemiology but will also help to guide vaccine development and predict vaccine efficacy across populations.

[N A J Med Sci. 2020;1(1):032-038. DOI: 10.7156/najms.2020.1301032]

Key Words: *SARS-CoV-2, COVID-19, human leukocyte antigen, major histocompatibility complex*

INTRODUCTION

When the novel coronavirus pandemic caught the world by surprise, of particular interest to the medical and scientific communities was the vast heterogeneity in susceptibility, severity, and presentation of SARS-CoV-2. While some patients report flu and cold-like symptoms, a particular subset develops a "cytokine storm", a potentially deadly reaction characterized by overactivation of the systemic inflammatory response.[1] Similarly, hematologic complications of the disease [including deep vein thrombosis (DVT) and disseminated intravascular thrombosis (DIC)] have been observed primarily in non-Chinese patient populations.[2,3] However, such demographic characteristics, while acting as effective predictors of disease vulnerability and prognosis, can fall short when attempting to determine specific outcomes on a community or personal level. Consequently, more specific biomarkers for SARS-CoV-2 are beginning to emerge, including genotypes of the Human Leukocyte Antigen (HLA), a key component in the adaptive immune response. HLA has been proposed to play a role in mediating viral susceptibility and disease presentation due to its central role in the human immune system.

Received: 09/04/2020; Revised: 10/04/2020; Accepted: 10/07/2020
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This review aims to explore the evidence base on the association between HLA and COVID19 susceptibility / symptom severity. Within the last few months, a review article that summarized the current literature on the relationship between HLA genotypes and coronavirus susceptibility was published by Alicia et al,[4] with a focus on SARS-CoV-1. The authors included case-control studies in Asian countries, as well as bioinformatics studies encompassing both SARS-CoV-1 and SARS-CoV-2. Due to increased international attention on the current pandemic, SARS-CoV-2 researchers are making rapid progress in expanding the knowledge base on the HLA / SARS-CoV-2 association. Since the publication of the previous review article, one additional case-control study,[5] two new cohort studies,[6,7] one additional bioinformatics study with in vitro validation,[8] as well as several functional studies using either case-control or case report design have been released specifically for SARS-CoV-2. Therefore, we believe that this topic warrants an updated review, with a focus on SARS-CoV-2, as we now have more data to compare risk/protective HLA alleles across the various coronavirus species. In this review, we offered an alternative and an updated framework for organizing the current studies on the HLA / SARS-CoV-2 association. First, we presented the available research on SARS-CoV-2 broken down by either protective / risk alleles or, in the absence of data regarding disease susceptibility, evidence for particularly strong binding affinity. Second, we performed a parallel comparison by

considering indirect supportive or conflicting evidence from studies on the HLA association with SARS-CoV-1 and Middle East respiratory syndrome coronavirus (MERS-CoV) as well as studies investigating other types of viral infections. Last, we provided a qualitative summary of the existing functional investigations on the role of HLA-DR and HLA-G in mediating inflammatory responses from SARS-CoV2 infection.

Table 1. Evidence for SARS-CoV-2 protective, risk, and high binding affinity alleles.

Allele	Supporting evidence (COVID 19)	Study design	Conflicting Evidence (COVID 19)	Evidence in other coronavirus studies?
Protective alleles				
HLA-A*02:02, HLA-B*15:03, HLA-C*12:03	Nguyen et al 2020: highest predicted peptide presenting ability	In silico	-	Oany et al, 2014: high binding affinity to spike protein epitope (B*15:03, C*12:03)
				Barquera et al, 2020: A*02:02, B*15:03 strongest SARS-CoV2 peptide binder
HLA-A*02:03, HLA-A*31:01	RomeroLopez et. al. 2020: lower incidence of COVID with higher allele frequency	In silico	-	Barquera et al, 2020: strongest A*02:03 SARS CoV 2 peptide binder
	Basu et al, 2020: both predicted to bind to epitope	In silico		
HLA-B*14, HLA -B*18, HLA -B*49	Correale et. al. 2020: allele frequency positively related with COVID-19 incidence	Observational	-	-
Risk alleles				
HLA-A*25:01, HLA-B*46:01, HLA-C*01:02	Nguyen et al 2020: fewest predicted binding peptides for COVID-19	In silico	-	Keicho 2009; Chen 2006: HLA-B*4601 associated with SARS susceptibility
HLA-B*15:27, HLA-C*07:29* (*based on 1 in COVID cohort)	Wang et al 2020: These alleles were found at higher rates in a COVID-19 positive population	Case control	-	-
HLA-A*03:02	Romero Lopez et. al. 2020: higher incidence of COVID with higher allele frequency	In silico	-	
HLA-A*24:02, HLA-DPA1*02:02, HLA-DPB1*05:01, HLA-DQB1*03:01, HLA-DRB4*01:01	Warren et al 2020:	Cohort		Oany et al, 2014: high binding affinity to spike protein epitope (A*24:02)
	Basu et al, 2020 (DRB4*01:01)	In silico		
HLA-A*25, HLA-B*08, HLA-B*44, HLA-B*15:01, HLA-B*51, HLA-C*01, HLA-C*03	Correale et. al. 2020	Cohort	-	-
High Binding Affinity Alleles (in silico or in vitro)				
HLA-A*02:01, HLA-B*40:01, HLA-DRA*01:01, HLA-DRB1*07:01, HLA-DRB1*04:01	Ahmed et. al. 2020: These are effective epitopes in both SARS-CoV and SARS-CoV2	In silico with in vitro validation		
HLA-DR/HLA-G (functional investigations)				
HLA-DR	Giamarellos-Bourboulis et al 2020: decreased HLA-DR in monocytes is associated with immunoparalysis	Case control /cohort study	Xu et al 2020: abundance of HLA-DR positive cells is associated with hyperactivation	Keicho 2009; Chen 2006: HLA-DR B1*1202 is associated with SARS susceptibility (conflicting)
	Spinetti et al 2020: severe COVID-19 disease is related to immunosuppression of central innate immune cells and reduced mHLA-DR expression.	-		Wang 2011: HLA-DR0301 decreases SARS
HLA-G	Zhang et al 2020: HLA-G levels decreased during the replication phase of COVID-19 and increased to corresponding cytokine levels.again after clearance, likely relating	Case report	-	-

Both the MHC class I and class II molecules are active mediators of humoral and cellular immunity through antigen presentation. Virus-specific B and T cells, which regulate the body's humoral and cellular immunity, are stimulated by antigen presentation. Whereas antibody response (IgM and IgG) has been documented for all coronaviruses,[9,10] cellular immunity plays a more prominent role.[11] Therefore, a better understanding of viral antigen presentation can elucidate COVID-19 pathogenesis and potentially help to explain the various degrees of appropriate immune response and immune over-activation (e.g. cytokine storm) that are present in different patients.

Similar to previous public health concerns, the current novel coronavirus pandemic disproportionally affects the communities that lack the economic and medical resources needed to mount a sufficient response. In the United States, this manifests in significantly higher hospitalization and mortality rates for African American, Hispanic, Pacific Islander, and Indigenous populations.[12,13] Due to these disparities being so closely associated with race and ethnicity, identifying particular genetic variations that influence SARS-CoV-2 susceptibility and severity between populations can have a substantial impact on the development of specific treatment and prevention models in underserved communities.

RESULTS

A Brief Historical Perspective

To date, there are a limited number of studies on the association between HLA and COVID-19, but there exists a wealth of literature on the relevance of HLA in other related coronaviruses such as SARS-CoV-1 and MERS-CoV, which all suggest the involvement of both MHC-I and MHC-II systems. Although studies on HLA association with COVID-19 are limited, the existing evidence from other related viruses provided promising clues for understanding pathophysiology and generating preventative and therapeutic efforts for COVID-19.

Both MHC I and II molecules appear to play a role in coronavirus susceptibility. Various types of HLA polymorphisms such as HLA-B*4601, HLA-B*5401, HLA-B*0703, HLA-DRB1*1202, and HLA-Cw*0801 are associated with SARS-CoV-1 susceptibility.[14-16] Specifically, HLA-B*4601 is strongly associated with SARS-CoV-1 severity in Asian populations.[16] On the other hand, alleles such as HLA-DR0301, HLA-Cw1502, and HLA-A*0201 decrease susceptibility to SARS-CoV-1 Infection.[5] In MERS-CoV infection, HLA-DRB1*11:01 and HLA-DQB1*02:0, which are variations of MHC II molecules, are associated with vulnerability to MERS-CoV.[17] Alleles that confer similar risk or protective effects in SARS-CoV-2 infection are summarized in **Table 1** and discussed extensively in the following sections.

SARS-Cov-2 Studies by Study Design

Case-control, cohort, and observational studies

Due to the relatively recent emergence of SARS-CoV-2, few published studies have investigated the relative frequencies of HLA alleles using a case-control study design. Despite multiple reports of case-control studies on other related coronaviruses, only one such study has been published specifically to SARS-CoV-2.[5] Wang et al compared the frequency of nine different HLA loci, genotyped in 82 Han subjects from Zhejiang, in SARS-CoV-2 positive patients with controls. The SARS-CoV-2 positive individuals were found to have a significantly higher incidence of the **HLA -C*07:29** and -**B*15:27** alleles.

An observational study conducted by Correale et al showed an association between HLA allele frequency distribution and COVID-19 occurrence in Italy. The data sample of HLA allele frequency was collected from the Italian Bone-Marrow Donors Registry, which was retrieved from 370,000 cohorts of volunteer donors. It was discovered that HLA-A*25, B*08, B*44, B*15:01, B*51, C*01, and C*03 showed positive log-linear association with COVID-19 incidence rate, and HLA-B*14, B*18, and B*49 showed an inverse log-linear association. Warren et al demonstrated primary observations on the bronchoalveolar lavage fluid samples of five patients at the early stage of the COVID-19 outbreak. HLA-A*24:02 allele was observed in four out of five (80%) patients. HLA class II DPA1*02:02 and DPB1*05:01 haplotype predicted in patients 1 to 4 (80%). Genes DQB1*03:01 and DRB4*01:01 were predicted in two of the five patients.

Table 2. In silico methodologies.

Reference	Methodology
Nguyen et al., 2020	SARS-CoV2 and SARS-CoV protein sequences from the NCBI RefSeq database were broken into 8 to 12-mers. Then binding affinity and global allele frequency data for 145 HLA alleles was predicted by netMHCpan v4.0
Romero-Lopez et al., 2020	The SARS-CoV-2 spike protein sequences was submitted to the TepiTool server from the IEDB Analysis Resource database in order to get the epitope prediction for the 27 most frequent HLA-A and B alleles. HLA class II epitopes were predicted with the IEDB MHC class II epitope prediction tool. The most immunogenic alleles were selected.
Ahmed et al., 2020	Identified epitopes on SARS-CoV that were experimentally confirmed by positive B or T cell assays, then compared the genetic sequences of the epitopes (proteins) to those of SARS-CoV2 and identified the sequences that had no mutations, indicating that they would almost certainly have the same binding as in SARS-CoV. Next they found the MHC molecules related to these epitopes and used the immune epitope database to estimate population coverage.

Bioinformatic in-silico studies

Three studies so far have explored the epidemiological association between HLA alleles and disease prevalence or used in silico/in vitro methods for HLA-allele functional prediction (see **Table 2** for summary of methods).[8,18,19] Nguyen et al conducted a comprehensive in silico analysis of viral peptide-MHC class I binding affinity across 145 HLA -A, -B, and -C genotypes for all SARS-CoV-2 peptides.[18] HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, indicating that individuals with this allele may be particularly susceptible to COVID-19. HLA-B*15:03 showed the greatest ability to present highly conserved SARS-CoV-2 peptides that are shared among human coronaviruses, suggesting the availability of cross-protective T-cell based immunity especially for individuals harboring such HLA alleles. Romero Lopez et al aimed to predict the most effective antigen-presenting HLA-class I and II alleles in top affected populations, 10 countries out of the top 14 countries with the highest number of confirmed cases by March 31st.[19] Epidemiological association between HLA allele frequency and cumulative occurrence of COVID-19 among countries was also demonstrated. The authors found a negative correlation between HLA-A*02:03 and A*31:01 frequencies and the cumulative incidence per 1 million inhabitants and a positive correlation with HLA-A*03:02. The authors concluded that, with this result, HLA-A*02:03 and A*31:01 were associated with better immunity against the infection and that HLA-A*03:02 can be considered as a risk factor. Ahmed et al screened B and T cell epitopes in the structural proteins of SARS-CoV-1 to identify identical epitopes on SARS-CoV-2 proteins.[8] Additionally, the authors performed a population analysis on the MHC alleles. They found five MHC alleles (HLA-A*02:01, HLA-B*40:01, HLA-DRA*01:01, HLA-DRB1*07:01, and HLA-DRB1*04:01) corresponded with 19 different epitopes and only 59.76% of the global population was determined to likely have an immune response to these epitopes.

Interestingly, despite multiple efforts to investigate risk or protection conferred by HLA alleles using epidemiological approaches, there is limited consensus on the potential functions of identified HLA alleles across studies. Romero-Lopez and Nguyen used similar methods, but none of the identified alleles overlapped. Also, these identified alleles showed a low level of overlap with previous studies on related coronaviruses, except for HLA-B*46:01, which was simultaneously identified in Nguyen et al as a risk allele and also previously found to be associated with SARS susceptibility.[15] However, it is encouraging that, based on Ahmed's work, a fraction of HLA alleles that have in vitro experimentally validated high binding affinities to SARS-CoV-1 epitopes also demonstrated strong binding affinities with SARS-CoV2 viral epitopes.

The roles of HLA-DR and HLA-G in SARS-COV2

HLA-DR is an MHC class II molecule, known to be involved in antigen presentation to helper T cells to facilitate the humoral immune response.[20] This is in contrast to MHC class I molecules, including HLA-A, -B, and -C, which present antigens on the surface of infected cells to mediate cell death via cytotoxic T-cells.[21] Due to the role of HLA-DR in the identification of extracellular pathogens, prior research has found that both individual HLA-DR allele composition and overall HLA-DR expression levels are effective markers for viral severity. In Hepatitis B and C, some HLA-DR alleles have been implicated in chronic infections, liver cirrhosis, and high viral load, while others are associated with viral clearance, slower disease progression, and reduced risk of chronic infection.[22] Likewise, the HLA-DR allele frequencies in patients suffering from SARS did not match that of healthy controls, indicating a link between HLA-DR and SARS susceptibility.[23] While specific HLA-DR alleles can have either a positive or negative effect on viral severity and susceptibility, reduced expression, particularly in monocytes, is often associated with an increased (or dysregulated) immune response.[24]

During respiratory syncytial virus infections, HLA-A, -B, and -C levels rise, as monocyte HLA-DR decreases, with more severe cases exhibiting even lower levels of expression. As of yet, the mechanism behind this reduction isn't fully understood, though pro-inflammatory cytokines are likely involved.[25] Similarly, reduced monocyte HLA-DR is associated with increased severity and decreased patient outcomes in liver disease,[26] septic shock,[27] and human cytomegalovirus.[28] This association between HLA-DR and immune dysregulation makes it an important molecule to consider when investigating the SARS-CoV-2 cytokine storm.

Three studies so far have explored the relationship of HLA-DR expression with COVID-19 severity.[29-31] Using a case-control study design, Giamarellos-Bourboulis et al investigated immune responses of 54 COVID-19 patients, including 28 cases of severe respiratory failure (SRF). The authors demonstrated critical functional significance of lower monocyte HLA-DR expression and elevated interleukin-6 (IL-6), which is known to decrease HLA-DR expression, as potential mediators of the aberrant immune response to COVID-19. Those with COVID-induced SRF exhibited either macrophage activation syndrome (MAS) or very low monocyte HLA-DR expression consistent with immunoparalysis. The authors described a pattern of immune dysregulation in SRF associated with acute COVID-19 infection characterized by IL-6-mediated low monocyte HLA-DR expression and lymphopenia which correlated with sustained cytokine production and hyper-inflammation. Using a prospective study design, Spinetti et al sought to investigate the level of the monocytic HLA-DR expression in COVID-19 patients in critical condition to understand the role of virus-induced immunosuppression. 16 COVID-19 positive patents, of which 9 Intensive Care Unit (ICU) patients with acute respiratory failure and 7 patients with primary hospitalization, were investigated in this preliminary observational study. All monocytic HLA-DR expressions of non-critically ill COVID-19 patients (n = 7) were normal, but 89% (8/9) of critically ill COVID-19 patients in ICU showed phenomenons of reduced monocytic HLA-DR expression. Thus the authors concluded

that severe COVID-19 disease is associated with immunosuppression of the innate immune system. In another case report, Xu et al presented both the medical treatments administered to a COVID-19 patient, as well as the pathological findings upon his death, with a focus on T cells rather than monocytes. The authors found a reduction in CD4 and CD8 T lymphocytes in the patient's peripheral blood, but the cells appeared to be hyper-activated with elevated expression of HLA-DR and CD38 (activated T cell marker).[32,33]

While there is not a well-defined or agreed upon "purpose" of HLA-G compared to other MHC molecules, HLA-G is known to have suppressive effects on the immune system. Its misregulation has been implicated in both autoimmune and infectious diseases. In many autoimmune disorders including Celiac Disease, Rheumatoid Arthritis, Lupus, Psoriasis, and Diabetes, HLA-G upregulation is related to disease onset and progression.[34] Likewise, increased HLA-G levels have been found in infections of HIV-1, human cytomegalovirus, HPV, and herpes simplex virus-1, likely as a way to avoid immune detection of infected cells.[34] This precedent implies a probable role in SARS-CoV-2 related immune dysfunction. Only one study has so far investigated HLA-G levels of COVID-19 patients.[35] A case study by Zhang et al reported the immune cell, cytokine, and HLA-G (including receptor) levels for a COVID-19 patient during his hospitalization. Overall, HLA-G levels decreased during the replication phase of COVID-19 and increased again after clearance, likely relating to corresponding cytokine levels.

DISCUSSION

Research on the association between HLA with COVID-19 is limited by heterogeneity in study design and the overall paucity of studies. There is a limited inter-study agreement, but overlaps of identified risk/protective alleles between COVID-19 studies, and with studies related to other SARS infections do exist, as summarized in **Table 1**. The list may continue to expand as more research on this topic emerges. HLA-A*02:02, HLA-B*15:03, HLA-C*12:03, HLA-A*02:03, and HLA-A*31:01 were protective alleles that were supported in multiple studies. Moreover, HLA-A*25:01, HLA-B*46:01, HLA-C*01:02, HLA-A*24:02, HLA-DPA1*02:02, HLA-DPB1*05:01, HLA-DQB1*03:01, and HLA-DRB4*01:01 were risk alleles that were supported in various studies.

Only a handful of case-control or cohort studies have been conducted and all are limited by relatively small sample sizes. Wang et al are the most stringent among the three observational studies with the inclusion of a proper control group, with 82 subjects included in the experimental group, and 3790 individual subject data, derived from previous studies from bone marrow donors, in the control cohort. Some conclusions may not be valid: for example, the reported "higher frequency" of HLA-C*07:29 in COVID-19 patients was based on HLA-C*07:29 being observed once in the experimental cohort and absent in the control group. Warren et al and Correale et al adopted a retrospective cohort study design without including control groups. Warren et al analyzed the HLA allele frequency of only five patients which seriously limit the validity of their findings. Correale et al examined the correlation between HLA allele distribution and COVID-19 occurrence using a large database, but the lack of a control cohort subject the study to various biases., All three studies are purely observational, so causation can only be inferred, calling for functional validations. The HLA genotypes that the three studies discovered did not overlap, which may be caused by differences in study design (samples taken from different countries with different genetic backgrounds), or simply sampling bias given the small sample sizes.

Due to the high cost and time-intensive nature of clinical studies, as well as the sheer number of HLA alleles and potential binding sites in SARS-CoV-2, many researchers have turned toward computer modeling based investigations. Both Nguyen et al and Romero-Lopez et al took in silico approaches where they modeled HLA alleles with SARS-CoV-2 proteins to determine binding affinity. While Romero-Lopez' analysis focused on the spike protein and compared potential binding sites to 27 common HLA-A and -B alleles, Nguyen took a broader approach, breaking down the entire SARS-CoV-2 proteome into 8 to 12 mers which could then be cross-referenced with 145 HLA alleles. Additionally, Nguyen used binding affinity as their primary metric for assessing the benefits or risks associated with various alleles, while Romero-Lopez also considered the T cell class I pMHC immunogenicity score when selecting the HLA alleles most likely to confer a protective advantage. These discrepancies in methodologies may account for the lack of overlap of protective alleles between the two studies. In addition to the in silico analysis, Romero-Lopez et al also compared the epidemiological data on cumulative COVID-19 occurrence with the distribution of HLA genotypes across populations. The population-level association cannot be readily applied on an individual level, and the frequency of the HLA alleles could have been subject to migration bias. Actions or policies implemented to restrain the epidemic were not also taken into account.

Similarly to Nguyen et al, another bioinformatic study on HLA binding affinity, Barquera et al, used entire proteomes (including that of SARS-CoV-2) broken up into 9 to 13 mers, compared against 405 HLA-A, -B, -C, and -DRB1 alleles. Unsurprisingly, Barquera and Nguyen conferred on some of their findings, with both papers citing HLA-A*02:02 and B*15:03 as some of the highest peptide-binding alleles for SARS-CoV-2. Less expected, however, is that Barquera et al also confirmed HLA-A*02:03 as being a strong binding allele, a conclusion shared by Romero-Lopez but not Nguyen. Due to the somewhat more limited scopes of Romero-Lopez' (and to a lesser extent, Nguyen's) papers, Barquera's more intensive analysis likely caught alleles missed by the other studies.

In contrast with the bioinformatic analyses mentioned up to this point, which utilized almost entirely in silico approaches,

Ahmed et al had a less direct design that combined both prior experimental evidence and predictive modeling. This study first identified SARS-CoV-1 epitopes that had been experimentally confirmed on T or B cell assays, then compared the protein sequences of these epitopes with the corresponding sequences in SARS-CoV-2. Once they identified fully conserved sequences, indicating that these epitopes are likely to remain unchanged, the authors found the corresponding HLA molecules for the original epitopes, allowing them to perform a population coverage analysis. Likely due in part to the roundabout identification of high binding affinity alleles, Ahmed didn't identify any MHC alleles that overlapped with those mentioned by the previous bioinformatics studies. The lack of convergence of Ahmed with the other studies, in addition to its inability to account for potential high binding affinity epitopes that arose in SARS-CoV-2, but not SARS-CoV-1, substantially reduces the efficacy of this analysis, and stronger consideration should be given to the studies that predicted SARS-CoV-2 peptide / MHC epitope binding affinity directly.

One additional bioinformatics study was identified, Basu et al, 2020, which provided supporting evidence for some of the alleles indicated by other papers. However, Basu et al investigated potential epitopes and corresponding HLA alleles specifically in terms of SARS-CoV-2 vaccine development targeting nonstructural protein 4, severely limiting its scope. Likewise, this article is a preprint, and as such has not been subject to peer review, meaning its findings should be taken with some caution. Nonetheless, Basu et al identified four alleles implicated in other studies, HLA-A*02:03, -A*31:01, -DRB1*07:01, and -DRB4*01:01 (in Romero-Lopez et al (both HLA-A alleles), Ahmed et al, and Warren et al, respectively) as MHC molecules likely to bind to nonstructural protein 4.

Three studies attempted to explore the pathophysiology of COVID-19 through functional analysis of HLA-DR mediated leukocyte activation. Giamarellos-Bourboulis et al is overall a well-designed study and is the only one with a control cohort, but it still contains a relatively small number of patients. Spinetti et al contains an even smaller sample size and does not include a control cohort, which limits the validity of their conclusions. The single case report by Xu et al at best provides a hint for future investigation, and its conclusion of T cell HLA-DR as a marker of immune activation is discordant with the observation by Giamarellos-Bourboulis et al, which did not observe a significant change in HLA-DR expression on CD4 T cells. The involvement of T Cell HLA-DR in COVID-19 requires further validation in a larger cohort. For future studies, the functional significance of HLA-DR in COVID-19 pathogenesis and disease severity can be established by animal models or in-depth in vitro studies using human cell lines/organoids. Also, given HLA-DR's involvement in both T cell and monocyte activation, future studies should simultaneously investigate both cell types to capture the whole picture of the innate and adaptive immune response. Regarding HLA-G, only one case report was published on its association with COVID-19 infection and the significance of its findings awaits independent, further corroboration from future studies.

The current novel coronavirus pandemic has exacerbated existing health disparities between racial, ethnic, and socioeconomic groups, perhaps best showcased by differential rates of hospitalization, intubation, and mortality. Certainly, these disparities are due in no insignificant part to varied access to healthcare, adequate living conditions, and employment-related benefits (such as the option to take a leave of absence or work remotely). However, there is still a substantial likelihood that genetic, epigenetic, or other biological factors may play a role in susceptibility to or severity of the SARS-CoV-2 virus. Previous studies have revealed considerable genetic components related to infectious disease susceptibility. For tuberculosis, certain polymorphisms of the NRAMP1 gene in West Africans are overrepresented in individuals positive for the disease.[36] Similarly, a specific allele of interferon-induced transmembrane protein-3 has been found to cause both higher susceptibility to and severity of the influenza virus, specifically in Caucasians from the United Kingdom, and Han Chinese.[37] Particularly in regards to COVID-19, racial disparities may be due in part to genetic differences in the androgen receptor which regulates ACE2, a key binding site that allows SARS-CoV2 to enter type II pneumocytes.[38] As such, future investigations into the ethnic disparities of SARS-CoV2 susceptibility/clinical presentation should focus on the interplay between economic, sociological, and biological factors.

In addition to demographic analysis, identification of particular HLA alleles can assist in vaccine development, demonstrating an extremely real-world application of this work. Distinguishing the SARS-CoV-2 related MHC molecules with both the highest binding affinity and population coverage should allow research into vaccine development to focus specifically on the peptides proven to cause an effective immune response. Similarly, identifying the alleles with substantially different expression patterns between regional and ethnic populations enables local health authorities to make decisions on which vaccine(s) may be best suited for their communities.

CONCLUSION

COVID-19 presents with substantial heterogeneity in disease severity and susceptibility, and the mechanisms of such heterogeneity remain unclear. Based on the hypothesis that the MHC/HLA system is key to antigen presentation and thus may affect the immune response to SARS-CoV-2, this review article examined the existing evidence for the involvement of the MHC/HLA system as potential effectors of disease susceptibility, and to a lesser extent, disease severity. We identified multiple HLA alleles associated with SARS-CoV2 risks or protection and provided a qualitative assessment of the strengths of the associations. Due to the recency of the COVID-19 outbreak, only a small number of studies exist on this topic. The cohort studies and case-control studies are overall limited by small sample sizes, and in-silico studies

have utilized varying methodologies leading to relatively poor reproducibility of the results across studies. Nonetheless, some HLA alleles were identified by multiple studies as significantly associated with COVID-19 risks/protection. These studies provided valuable, though preliminary insights into the potential pathophysiology and epidemiology of the COVID-19 outbreak, and aid in efforts of vaccine development.

CONFLICT OF INTEREST

None.

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