Plausible Influence of HLA Class I and Class II Diversity on SARS-CoV-2 Vulnerability

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ABSTRACT: Severe acute respiratory syndrome CoV-2 (SARS-CoV-2) caused the global coronavirus disease 2019 (COVID-19) pandemic, which adversely affected almost all aspects of human life and resulted in the loss of millions of lives, while affecting nearly 0.67 billion people worldwide. SARS-CoV-2 still poses a challenge to the healthcare system as there are more than 200,000 active cases of COVID-19 around the globe. Epidemiological data suggests that the magnitude of morbidity and mortality due to COVID-19 was low in a few geographical regions and was unpredictably higher in a few regions. The genetic diversity of different geographical regions might explain the sporadic prevalence of the disease. In this context, human leukocyte antigens (HLA) represent the most polymorphic gene-dense region of the human genome and serve as an excellent mini-genome model for evaluating population genetic diversity in the context of susceptibility and progression of various diseases. In this review, we highlight the plausible influence of HLA in susceptibility, severity, immune response, and designing of epitope-based vaccines for COVID-19. Further, there is a need for extensive investigations for illustration and clarification of the functional impact of HLA class I and II alleles in the pathogenesis and progression of SARS-CoV-2.

KEY WORDS: HLA, COVID-19, SARS-CoV-2, susceptibility

I. HUMAN LEUKOCYTE ANTIGENS: A HALLMARK OF DISEASE VULNERABILITY

Coronavirus disease 2019 (COVID-19) is a global public health emergency caused by a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It was first reported as a pandemic by the World Health Organization (WHO) on March 11, 2020. WHO has confirmed 587 million confirmed cases and 6.4 million deaths across the globe.[2,3] This virus belongs to the β-coronavirus family and is zoonotic, which imposes a serious challenge to establish preventive and treatment strategies. As per recent studies, this virus has a high magnitude of infection and transmission as compared to severe acute respiratory syndrome (SARS-CoV) and middle east respiratory syndrome coronaviruses (MERS-CoV).[4] Thus, it is a global health concern and emphasizes the urgent need to understand the mechanism of its destructive dissemination among certain geographical regions and populations.

As of now, various studies have attempted to analyze host–pathogen interactions along with immune parameters involved in clinical progression. However, the nascent available information is completely lacking key aspects of the genetically defined population-specific immune correlates. Particularly, the major histocompatibility complex (MHC) encoding the human leukocyte antigens (HLA) represents the most polymorphic gene-dense region of the human genome (loci 6p21.3, with ~ 36,000 HLA alleles) and serves as an excellent mini genome model towards evaluating population genetic diversity in the context of susceptibility and progression of various diseases.[5] Besides high polymorphism, tight linkage among various HLA loci along with the non-random association of its diverse alleles is of major significance in population genetics. Incidentally, this genomic region is also known to be the

significantly linked genetic loci in most of the genome-wide association studies on various infectious and autoimmune diseases as well as cancers.[6,7] Most importantly, the HLA is a hallmark for the initiation of both cellular and humoral adaptive immune responses for immune surveillance because the encoded molecules comprise the antigen presentation system. The population-specific HLA diversity has been consistently evolving over the years under diverse population-specific microbial and geographical pressure. The constant evolutionary pressure on this genomic region along with its biological relevance in orchestrating the adaptive immune responses rationalize that the population-specific allelic, genotypic, and haplotypic differences across world populations might explain the observed differential vulnerability to COVID-19 in terms of magnitude of morbidity and severity.

On these lines, selected studies have proposed that variability across the HLA class I and II genes can influence the viral acquisition, its transmissibility, and the severity of COVID-19.[8–10] This highly polymorphic system is known to facilitate genetic predisposition towards many infectious viral diseases such as HIV, influenza, and hepatitis,[11,12] including SARS-CoV-2. HLA plays various important roles in infectious diseases including genetic susceptibility, disease severity, immune response, and in the design of epitope-based vaccine (Fig. 1), and needs to be assessed further in the context of COVID-19.

II. EVIDENCE OF HLA CLASS I IMPACT ON COVID-19 RISK

SARS-CoV, from the original SARS outbreak (2002–2003), and SARS-CoV-2 exhibit ~ 72% nucleotide sequence similarity in the spike (S) protein, the key surface glycoprotein that interacts with host cell receptors.[13] It was mainly spread in Asia, especially in China, which suggested a regional/territorial or ethnic-oriented infection and suggested a significant contribution of prevailing HLA alleles in that region; e.g., Lin et al. observed that individuals carrying HLA-B*46 were more vulnerable to SARS-CoV infection.[14] This study reported increased frequency of the HLA-B* 46:01 allele in the "probable SARS infected" patient group and further, a significant increase was also reported in severe cases of SARS, which indicated the association of HLA-B*46:01 with the severity of SARS infection in Asian populations. Also, HLA-B*46:01 distribution in Southeast Asia imposes an increased risk of SARS-CoV infection. Another study reported

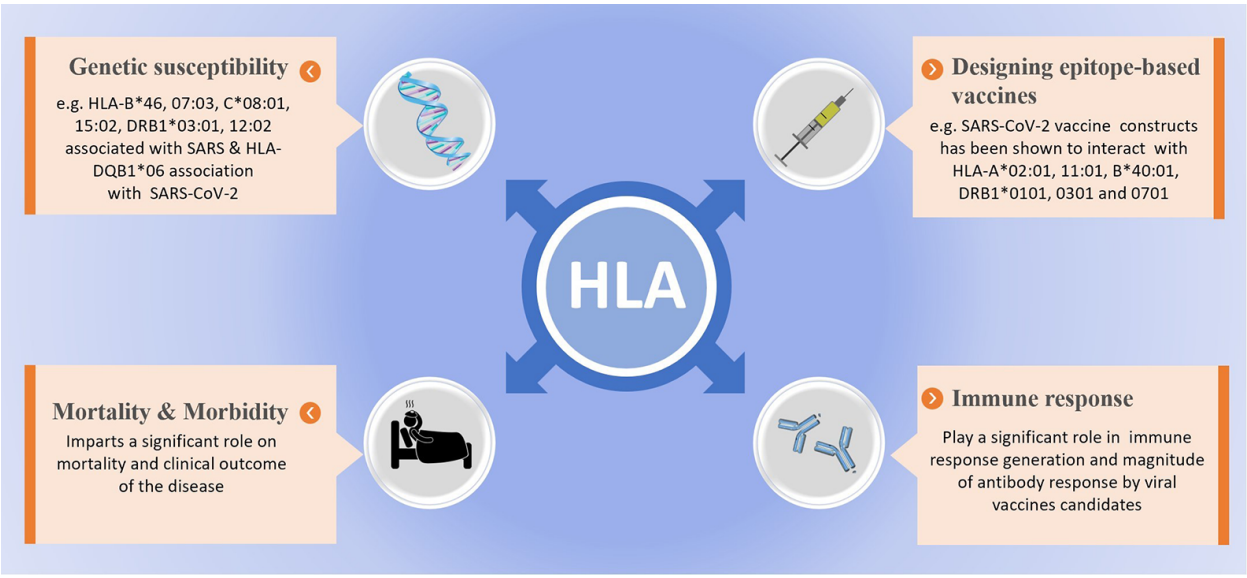

FIG. 1: Plausible association of HLA class I and II with susceptibility and severity of COVID-19

the association of HLA-B*07:03 and B60 coinheritance and increased risk of SARS in the Hong Kong Chinese population.[15] Nguyen et al. found that HLA-B*46:01 had the fewest predicted binding peptides for SARS-CoV-2, which suggests the genetic predisposition of these individuals towards COVID-19.[16] On the contrary, they observed that HLA-B*15:03 had the most potential in presenting highly conserved SARS-CoV-2 peptides that are shared among common human coronaviruses and emphasized its role in cross-protective T-cell-based immunity. Mechanistically, specific HLA genotypes could differentially affect SARS-CoV antigen presentation to induce the T-cell mediated antiviral response and this might explain the heterogeneity of clinical outcomes. Further, plausibly the viral antigen could noncovalently and/or reversely bind to certain HLA molecules, outside the antigen binding cleft of the MHC and thus indirectly modulate the tertiary immune synapse. This requires further exploration, as to the best of our knowledge, no definitive HLA associations support this hypothesis as yet. Additionally, the observed HLA allelic associations could be attributed to yet-unknown causal genetic loci that may be in linkage disequilibrium with observed risk/protection conferring HLA alleles. The linkage of this yet-unknown causal loci with observed risk/protection conferring HLA allele could vary further in a population-specific manner, resulting in heterogeneity in HLA allelic associations with COVID-19 vulnerability across various populations.

To unravel the impact of HLA, a publicly accessible database of epitopes that were predicted to bind any class I HLA protein across the entire SARS-CoV-2 proteome has been generated. Nerli and Sgourakis have performed structure-based modeling of SARS-CoV-2 peptide/HLA-A02 antigen and the models generated are available in an online database (https://rosettamhc.chemistry.ucsc.edu).[17] HLA-B*46 allele, which was associated with increased risk towards SARS-CoV during the SARS outbreak (2002–2003), has been suggested to play a protective role in the Indian population during the SARS outbreak in 2003.[18] This population-specific heterogeneity in HLA allelic associations with COVID-19 vulnerability could be attributed to the linkage of HLA-B*46 to yet unknown causal loci differentially in a population-specific manner. To this end, significantly high HLA diversity in the Indian population has been discussed[19] and the plausible occurrence of novel HLA alleles and haplotypes could be attributed to observed lower morbidity and mortality rates as compared to other countries such as UK, USA, Italy, Spain, and others.[20]

Another study has reported a significant increase in HLA-B*07:03 frequency in SARS patients[14] whereas the higher frequency of HLA-B*15:02 did not remain significant in SARS resistant group.[21] Yuan et al.[22] and Xiong et al.[23] did not find any significant association between HLA-A and -B in SARS patients from Hong Kong China and Guangdong. Other studies have reported HLA-C*08:01 and HLA-C*15:02 as a significant susceptibility marker for SARS patients from Taiwan.[24,25] HLA-B*15, HLA-B*51:01, and HLA-A*26:01 have been reported to impart increased survival in Egyptian and UAE COVID-19 patients, respectively.[26,27]

In the recent past, a study of 45 Spanish SARS-CoV-2 patients suggested an association of heterozygosity with disease severity.[28] Further, analysis of the correlation between HLA supertypes (a group of HLA alleles with almost identical peptide binding preferences) and SARS-CoV-2 peptide affinity revealed significant identification of peptides by A2 supertypes as compared to A1 and A3. Also, the C1 supertype showed a higher recognition frequency for peptide recognition. Most recently, a systematic review has been performed to analyze HLA alleles associated with COVID-19 susceptibility and severity in different populations and HLA-A*30:02 has been observed as a common allele among COVID-19 populations.[29] On the other hand, HLA-B*15:01 has been proposed as a protective allele in asymptomatic COVID-19 patients.[30]

Besides, a direct role in antigen presentation, HLA class I along with killer cell immunoglobulin-like receptors (KIR) acts as a key regulator of natural killer cell education/licensing towards the targeted killing of viral infected or tumor cells. KIRs are expressed on NK cells and regulate their activity through the identification of human leukocyte antigen (HLA) class I on the target cells. KIR receptors differ in number and identity in different individuals

and their expression is efficiently regulated, which determines the activating or inhibiting role of NK cells. Both HLA and KIR are highly polymorphic molecules and a wide array of permutations of HLA-KIR expression triggers differences in binding affinities and further affects the activation of NK cells during viral infection.[31] This warrants cumulative analysis of the HLA-KIR axis to identify novel immune correlates of COVID-19 vulnerability. Previously, it has been reported that suppressed KIR2DL2 gene expression accounts for increased susceptibility to SARS-CoV.[32]

III. HLA CLASS II AND GENETIC PROPENSITY TO COVID-19

Previous studies and a few recent reports confirm the correlation between the predominance of SARS-CoV infection and HLA class II alleles in different populations. In SARS infection, HLA-DRB1*0301 and HLA-DRB1*12:02 have been reported to confer protection and susceptibility towards SARS-CoV infection.

During the 2002–2003 SARS outbreak, the association of HLA-DRB1*03:01 was explored to find out genotypes associated with susceptibility and resistance in the Hong Kong Chinese population.[15] In this study, it was observed that HLA-DRB1*0901 was present in higher frequency in SARS patients but did not reach statistical significance. Whereas HLA-DRB1*0301 showed lower frequency in the patient group, indicating a protective role, and it was suggested that there might be an impaired CD4+ T cell response in HLA-DRB1*0301 negative patients. Later, the same research group performed HLA genotyping of 90 serologically confirmed SARS patients from the Chinese population and observed equal distribution of HLA-DRB1*0301 in both infected and non-infected groups from the local Chinese population.[21] In the same study, DRB4*01010101 was found in significantly higher frequency in the infected group but it did not remain significant post-Bonferroni correction. The marginal negative association of HLA-DRB1*13 has also been observed in the infected group as compared to the uninfected group ($p = 0.0069$) in the Vietnamese population. HLA-DRB1*0301 has also been reported to impart protection against SARS infection in the Taiwanese population.[25] As per the most recent data, HLA-DRB1*0301 was not observed in NGS-based screening of HLA genotypes in the Chinese population.[33]

HLA-DRB1*03:01 has been shown in the predominantly Indian population[34] and has been associated with type 2 diabetes mellitus in the South Indian population.[35] It is also considered as one of the -DRB1 alleles, which could represent an epicenter for the admixture of African, North-East Indian, and South Indian populations.[36] Collectively, this data proposes the role of this allele in imposing a protective effect against SARS-CoV-2 in the Indian population.

Another HLA class II allele, HLA-DRB1*12, was observed in higher frequency in the control group as compared to SARS-confirmed cases from Guangdong, China. It was observed that allele frequency of -DRB1*12 was 32.6% in 95 SARS and 22.8% in 403 controls ($p < 0.046$), which did not remain significant after multiple statistical comparisons and thus indicated a lack of association of -DRB1*12:02 with SARS-CoV infection.[23] On the other hand, in another study of 44 SARS-infected patients, 103 staff members of the same hospital as the control group who had come into contact with SARS patients but were SARS negative, confirmed the significant association of -DRB1*12:02 in SARS-CoV-positive Vietnamese population.[37] The same study also observed no significant association of HLA-DRB1*1301, *1302, and *1303 with susceptibility or resistance against SARS. Interestingly, one of the most frequent haplotypes carrying the HLA-DRB-12*02 allele has been observed in the Vietnamese population.[38] Most recently, -DRB1*12:02 has been observed in low frequency and found statistically insignificant in an NGS-based HLA typing of 82 Chinese COVID-19 confirmed cases.[33]

Interestingly, HLA-DRB1*12 has been previously reported to be predominant in the Thai population,[39] Vietnamese,[38] the isolated Han population in Southwest China,[40] and Koreans.[41]

Wang et al. reported a higher frequency of HLA-DRB1*04:06 in 82 Chinese SARS-CoV-2

positive patients but observed it to be statistically insignificant.[33] HLA-DR, an MHC class II surface receptor, is an important activation marker in severely infected COVID-19 patients and it has been reported to be increased in extremely severe patients compared with mild patients,[42] whereas, in another study of severely infected cases, it was found that most of the severe respiratory failure patients suffered from immune dysregulation dominated by low expression of HLA-DR on CD14 monocyte due to elevated IL-6 levels.[43] Further, the crucial role of HLA class I, II, and III in viral infections including SARS-CoV-2 has been highlighted by Kachuri et al.,[34] who performed genome-wide association studies (GWAS) and transcriptome-wide association studies (TWAS). In TWAS analysis, an association of HLA class II alleles has been observed for HLA-DRB5 and HLA-DRB1 for the Epstein–Barr virus (EBV) in a European cohort. Also, DRB1*15:01 (OR = 1.33, CI 1.01–1.74) was observed to be associated with an increased probability of testing positive for SARS-CoV-2. Another study to illustrate the significance of HLA in SARS-CoV-2 infection worldwide evaluated binding affinities of 438 HLA proteins to complete proteomes of seven pandemic viruses including SARS-CoV-2.[44] This study reported that most SARS-CoV-2 peptides bind to HLA class II molecules as compared to class I. Further, it has been observed that approximately half of the HLA-DR molecules are not strong binders, but the proportion of HLA-DR (6.4%) is higher as compared to HLA-DQ (null). Overall, it has been reported that HLA-DR displays heterogeneous kinds of binding affinities towards SARS-CoV-2.[44] HLA-DRB4*01:01 has also been reported as a risk factor in early stage COVID-19 patients in China.[45] Increased frequency of HLA-DRB1*15, HLA-DRB1*10, and DRB1*11 has been observed in COVID-19 patients in the United Kingdom, but did not reach statistical significance.[46] Taken together, these studies suggest that impaired ability of HLA molecules to present the viral peptides might be one of the explanations to clarify the role of risk and protective alleles in SARS-CoV-2 infection and progression of the disease.

Taken together, few studies have reported the association between HLA and susceptibility towards COVID-19 (Fig. 2) but these studies provide a significant plausible role of HLA in COVID-19.[47–58]

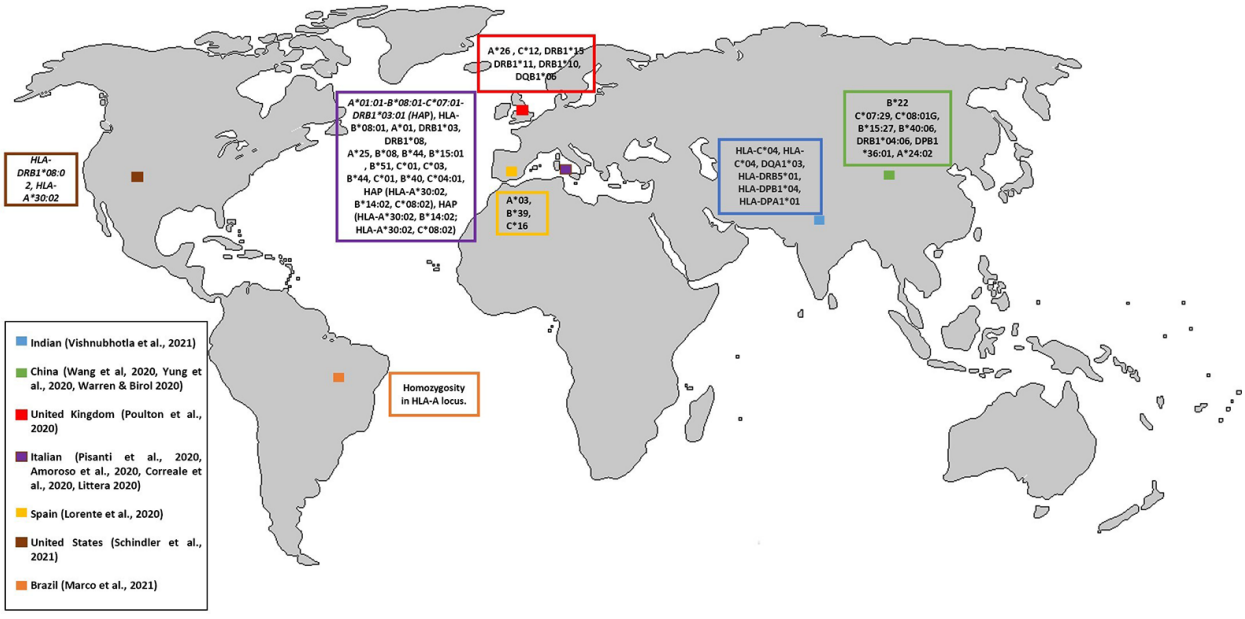

FIG. 2: Representative map to show various HLA alleles associated with COVID-19 in different populations. (Map not to scale).

IV. HLA AND IMMUNOINFORMATIC CORRELATES OF SARS-COV-2 VULNERABILITY

In the recent past, several studies have discussed and exemplified the role of host genetic factors, HLA in particular, for the development of vaccine candidates and to provide better insight into the role of HLA class I and II in the pathogenesis and progression of COVID-19. To this end, various studies have analyzed available experimentally derived B-cell and T-cell epitopes of SARS-CoV-2 using an immunoinformatics approach to develop potential vaccine candidates. Evaluation of the association of MHC alleles with these epitopes provides potent targets for vaccine development. Two distinct HLA class, I alleles (HLA-A*02:01 and HLA-B*40:01) have been observed to be associated with 19 epitopes which were present in either the N or S protein of SARS-Co-V-2.[59] Another immunoinformatic study suggested the interaction of HLA class I alleles with putative T-cell epitopes of SARS-CoV-2 (FTIGTVTLK and ITLCFTLKR), ITLCFTLKR epitope of the ORF-7A protein showed significant binding with HLA-A*11:01, HLA-A*68:01).[60] In the recent past, multiple studies have reported the interaction of various T-cell epitopes and their interactions with HLA class I alleles to design epitope-based vaccines using the immunoinformatics approach.[61–64]

Few studies have been done to identify HLA class II epitopes, HLA-DRB1*01:01 has been observed to interact with potent epitopes with 91.94% of global accumulated population coverage and 78.23% accumulated population coverage in China.[59] Another similar study predicted two potent epitopes, ITLCFTLKR and VYQLRARSV, which showed interactions with HLA-A*68:01 and HLA-DRB1*07:01 complexes, respectively. Both epitopes showed positive results for molecular dynamics and simulation analysis.[60] Similarly, another immunoinformatics study suggested epitope-based subunit vaccine conferring protection against SARS-CoV-2, and out of three selected vaccine constructs, epitopes present in the best vaccine construct interacted with DRB3*0202, DRB5*0101, DRB1*0101, DRB3*0101, DRB1*0401, and DRB1*0301.[64] Liu et al.[61] have provided an evaluation tool, EvalVax, to design vaccines based on the expression of viral proteins and their MHC interactions. This study observed that S protein and the S1 subunit are both limited in their predicted ability to provide robust population coverage for MHC class II display of more than five viral epitopes, which emphasizes the requirement of additional peptide components for consistent CD4+ T cell activation throughout the population if vaccine comprised of S protein or its subunits.[61] Another study predicted seven efficient epitopes from the global infected population, and structure and docking analysis confirmed that these epitopes showed high binding affinity to both MHC class I and II.[65]

Overall, these immunoinformatic approaches could be a benchmark for the prediction of immunodominant epitopes and their interplay with HLA class II to facilitate the rapid process of a safe and effective vaccine for COVID-19.

V. HLA RESTRICTED SARS-COV-2 PEPTIDES: PLAUSIBLE MECHANISTIC RELEVANCE

Recognition of viral antigens by HLA class I and II alleles accounts for the heterogeneity of T-cell response towards SARS-CoV-2 infection. Studies have shown various HLA class I alleles interacting with peptides from non-structural proteins of SARS-CoV-2, and HLA-A*02:01 has been reported as one of the most common interacting alleles.[66] Whereas another study has shown that spike peptides FTISVTTEI, MIAQYTSAL, and nucleocapsid peptide KTFPPTEPK showed higher binding affinities and interacted with HLA-B15:03, HLA-C12:03, and HLA-A02:02, respectively.[67] More recently, Augusto et al.[30] observed the mechanistic basis of a strong association between HLA-B*15:01 and asymptomatic infection.[30] This group found that the T cells from pre-pandemic samples from B*15:01 carrying individuals showed response to immunodominant SARS-CoV-2 S-derived peptide NQKLIANQF. The crystal structure of HLA-B*15:01-peptide complexes revealed cross reactivity due to shared similarity with peptides derived from seasonal coronaviruses, providing the molecular basis for HLA-B*15:01 mediated pre-existing immunity.

MHC class II–restricted CD4+ T cells regulate immune response and are crucial for the development of epitope-based vaccines and effective immunotherapies. As discussed previously, HLA-DRB1*03:01, 04:06, 12:02, and 15:01 have been associated with increased risk towards SARS-CoV-2 infection, but the mechanistic approach to understanding their interaction with SARS-CoV-2 peptides is not well understood. Most recently, an immunoinformatic approach has been applied to identify the interaction of SARS-CoV-2 peptides and HLA class I and II and it has been observed that HLA-DRB1*03:01 is one of the most common alleles interacting with peptides of non-structural protein (NSP) of SARS-CoV-2.[66] Whereas in another study, HLA-DRB1*15:01 was observed to be interacting with the most promising peptides from both nucleocapsid and spike glycoprotein of SARS-CoV-2.[67] Also, the Spike peptide EVFNATRFASVYAWN showed the highest binding affinity with HLA-DPA1*01:03/DPB1*02:01, HLA-DQA1*01:02/DQB1*06:02, and HLA-DRB1. Additionally, HLA-DRB1*03:01 and *15:01 have been investigated in rhinovirus infection in humans and it was observed that these two alleles present capsid protein VP2 peptide (NEKQPSDDNWLNFDGTLLGN) and (SNNSATLIVPYVNAVPMDSM) to Th1 cells, respectively, and facilitate viral clearance.[68] Most recently 438 HLA proteins were screened to investigate their binding affinities with pandemic human viruses including influenza, HIV, and coronaviruses and it was observed that among the HLA class II alleles DRB1*07:01, 11:14, 13:02 showed the strongest binding affinity towards all respiratory viruses.[44]

VI. CONCLUDING REMARKS

Evolving evidence suggests the influence of select HLA class I and class II alleles on SARS-CoV-2 vulnerability. Immunoinformatic tools and a few mechanistic studies dissecting the crystal structure of the SARS-CoV-2 peptide-MHC ternary complex suggest a functional and mechanistic impact of the human antigen presentation system in the differential genetic propensity to COVID-19. Nevertheless, most of these studies involve a limited number of individuals and are conducted in limited populations, which warrants further, extensive investigations to unravel the functional impact of HLA class I and II alleles in the pathogenesis and progression of SARS-CoV-2. It is also imperative to understand the population coverage of these alleles in the context of SARS-CoV-2 for the development of better vaccine candidates and therapeutics.

REFERENCES

1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus (COVID-19) outbreak. J Autoimmun. 2020;109:1–4.
2. WHO. Coronavirus disease (COVID-19) situation report – 181 [Internet]. 2020. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
3. Naz S, Zahoor M, Sahibzada MUK, Ullah R, Alqahtani AS. COVID-19 and SARS-CoV-2: Everything we know so far – a comprehensive review. Open Chem. 2021; 19(1):548–75.
4. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. 2020;27(2):1–4.
5. Mosaad YM. Clinical role of human leukocyte antigen in health and disease. Found Scand J Immunol. 2015;283–306.
6. Muñiz-Castrillo S, Vogrig A, Honnorat J. Associations between HLA and autoimmune neurological diseases with autoantibodies. Autoimmun Highlights. 2020;11(1):2.
7. Debebe BJ, Boelen L, Lee JC, Thio CL, Astemborski J, Kirk G, Khakoo SI, Donfield SM, Goedert JJ, Asquith B. Identifying the immune interactions underlying HLA class I disease associations. Elife. 2020;9:e54558.
8. Migliorini F, Torsiello E, Spiezia F, Oliva F, Tingart M, Maffulli N. Association between HLA genotypes and COVID-19 susceptibility, severity and progression: A comprehensive review of the literature. Eur J Med Res. 2021;26(1):84.
9. Deb P, Zannat K, Talukder S, Bhuiyan AH, Jilani MSA, Saif-Ur-Rahman KM. Association of HLA gene polymorphism with susceptibility, severity, and mortality of COVID-19: A systematic review. HLA. 2022;99(4):281–312.
10. Gutiérrez-Bautista JF, Rodriguez-Nicolas A, Rosales-Castillo A, López-Ruz MÁ, Martín-Casares AM, Fernández-Rubiales A, Anderson P, Garrido F, Ruiz-Cabello F, López-Nevot, MÁ. Study of HLA-A, -B, -C, -DRB1 and -DQB1 polymorphisms in COVID-19 patients. J Microbiol Immunol Infect. 2022;55(3):421–7.
11. Luckey D, Weaver EA, Osborne DG, Billadeau DD, Taneja V. Immunity to influenza is dependent on MHC II polymorphism: Study with 2 HLA transgenic strains. Sci Rep. 2019;9(1):19061.

12. Blackwell JM, Jamieson SE, Burgner D. HLA and infectious diseases. Clin Microbiol Rev. 2009;22(2):370 LP – 385.
13. Zhang YZ, Holmes EC. A genomic perspective on the origin and emergence of SARS-CoV-2. Cell. 2020;181(2): 223–7.
14. Lin M, Tseng HK, Trejaut JA, Lee HL, Loo JH, Chu CC, Chen PJ, Su YW, Lim KH, Tsai ZU, Lin RY. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. BMC Med Genet. 2003;4(1): 1–7.
15. Ng MH, Lau KM, Li L, Cheng SH, Chan WY, Hui PK, Zee B, Leung CB, Sung JJ. Association of human-leukocyte-antigen class I (B* 0703) and class II (DRB1* 0301) genotypes with susceptibility and resistance to the development of severe acute respiratory syndrome. J Infect Dis. 2004;190(3):515–8.
16. Nguyen A, David JK, Maden SK, Wood MA, Weeder BR, Nellore A, Thompson RF. Human leukocyte antigen susceptibility map for severe acute respiratory syndrome coronavirus 2. J Virol. 2020;94(13):10–128.
17. Nerli S, Sgourakis NG. Structure-based modeling of SARS-CoV-2 peptide/HLA-A02 antigens. BioRxiv. 2020;(2019):1–13.
18. Umapathy S. Absence of HLA B*46 in Indian population: Could it be the cause for protection from SARS epidemic? J Assoc Phys India. 2004;52:760–1.
19. Saxena A, Sharma G, Tyagi S, Mourya M, Coshic P, Tiwari PK, Mehra NK, Kanga U. HLA-A* 02 repertoires in three defined population groups from North and Central India: Punjabi Khatries, Kashmiri Brahmins and Sahariya tribe. HLA. 2019;93(1):16–23.
20. Mehra NK, Sharma G. Indian population could have intrinsic immunity to resist COVID-19 challenge [Internet]. 2020. Available from: https://www.immunopaedia.org.za/breaking-news/indian-population-could-have-intrinsic-immunity-to-resist-covid-19-challenge/
21. Ng MH, Cheng SH, Lau KM, Leung GM, Khoo US, Zee BC, Sung JJ. Immunogenetics in SARS: A case-control study. Hong Kong Med J. 2010;16(5 Suppl 4):29–33.
22. Yuan FF, Velickovic Z, Ashton LJ, Dyer WB, Geczy AF, Dunckley H, Lynch GW, Sullivan JS. Influence of HLA gene polymorphisms on susceptibility and outcome post infection with the SARS-CoV virus. Virol Sin. 2014;29(2):128–30.
23. Xiong P, Zeng X, Song MS, Jia SW, Zhong MH, Xiao LL, Lan W, Cai C, Wu XW, Gong FL, Wang W. Lack of association between HLA-A,-B and-DRB1 alleles and the development of SARS: A cohort of 95 SARS-recovered individuals in a population of Guangdong, southern China. Int J Immunogenet. 2008;35(1):69–74.
24. Chen YM, Liang SY, Shih YP, Chen CY, Lee YM, Chang L, Jung SY, Ho MS, Liang KY, Chen HY, Chan YJ. Epidemiological and genetic correlates of severe acute respiratory syndrome coronavirus infection in the hospital with the highest nosocomial infection rate in Taiwan in 2003. J Clin Microbiol. 2006;44(2):359–65.
25. Wang SF, Chen KH, Chen M, Li WY, Chen YJ, Tsao CH, Yen MY, Huang JC, Chen YM. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. Viral Immunol. 2011;24(5): 421–6.
26. Abdelhafiz AS, Ali A, Fouda MA, Sayed DM, Kamel MM, Kamal LM, Khalil MA, Bakry RM. HLA-B* 15 predicts survival in Egyptian patients with COVID-19. Hum Immunol. 2022;83(1):10–6.
27. Alnaqbi H, Tay GK, Jelinek HF, Francis A, Alefishat E, Chehadeh SE, Saeed AT, Hussein M, Salameh L, Mahboub BH, Uddin M. HLA repertoire of 115 UAE nationals infected with SARS-CoV-2. Hum Immunol. 2022;83(1):1–9.
28. Iturrieta-Zuazo I, Rita CG, García-Soidán A, de Malet Pintos-Fonseca A, Alonso-Alarcón N, Pariente-Rodríguez R, Tejeda-Velarde A, Serrano-Villar S, Castañer-Alabau JL, Nieto-Gañán I. Possible role of HLA class-I genotype in SARS-CoV-2 infection and progression: A pilot study in a cohort of COVID-19 Spanish patients. Clin Immunol. 2020;219:108572. doi: 10.1016/j.clim.2020.108572.
29. Fakhkhari M, Caidi H, Sadki K. HLA alleles associated with COVID-19 susceptibility and severity in different populations: A systematic review. Egypt J Med Hum Genet. 2023;24(1):10.
30. Augusto DG, Murdolo LD, Chatzileontiadou DS, Sabatino Jr JJ, Yusufali T, Peyser ND, Butcher X, Kizer K, Guthrie K, Murray VW, Pae V. A common allele of HLA is associated with asymptomatic SARS-CoV-2 infection. Nature. 2023;620(7972):128–36.
31. de Wit J, Borghans JAM, Kesmir C, van Baarle D. Editorial: Role of HLA and KIR in viral infections. Front Immunol. 2016;7:286.
32. Wang C, Xia CQ. The involvement of natural killer cells in the pathogenesis of severe acute respiratory syndrome. Am J Clin Pathol. 2004;121(4):507–11.
33. Wang W, Zhang W, Zhang J, He J, Zhu F. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). HLA. 2020:194–6.
34. Kachuri L, Francis SS, Morrison M, Bossé Y, Cavazos TB, Rashkin SR, Ziv E, Witte JS. The landscape of host genetic factors involved in infection to common viruses and SARS-CoV-2. medRxiv. 2020 May 30.
35. Chinniah R, Vijayan M, Sivanadham R, Ravi PM, Paneerselvam D, Karuppiah B. Association of HLA-A, B, DRB1* and DQB1* alleles and haplotypes in south Indian T2DM patients. Gene. 2016;592(1):200–8.
36. Nandakumar R. The genetic diversity of HLA DRB1* alleles among Indian and African populations. World Sci News. 2018;114:15–29.

37. Keicho N, Itoyama S, Kashiwase K, Phi NC, Long HT, Van Ban V, Hoa BK, Le Hang NT, Hijikata M, Sakurada S, Satake M. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. Hum Immunol. 2009;70(7): 527–31.
38. Hoa BK, Hang NT, Kashiwase K, Ohashi J, Lien LT, Horie T, Shojima J, Hijikata M, Sakurada S, Satake M, Tokunaga K. HLA-A,-B,-C,-DRB1 and-DQB1 alleles and haplotypes in the Kinh population in Vietnam. Tissue Antigens. 2008;71(2):127–34.
39. Satapornpong P, Jinda P, Jantararoungtong T, Koomdee N, Chaichan C, Pratoomwun J, Na Nakorn C, Aekplakorn W, Wilantho A, Ngamphiw C, Tongsima S. Genetic diversity of HLA class I and class II alleles in Thai populations: Contribution to genotype-guided therapeutics. Front Pharmacol. 2020;11:78.
40. Yao Y, Shi L, Shi L, Matsushita M, Yu L, Lin K, Tao Y, Huang X, Yi W, Oka T, Tokunaga K. Distribution of HLA-A,-B,-Cw, and-DRB1 alleles and haplotypes in an isolated Han population in Southwest China. Tissue Antigens. 2009;73(6):561–8.
41. Song EY, Park H, Roh EY, Park MH. HLA-DRB1 and -DRB3 allele frequencies and haplotypic associations in Koreans. Hum Immunol. 2004;65(3):270–6.
42. Wang F, Hou H, Luo Y, Tang G, Wu S, Huang M, Liu W, Zhu Y, Lin Q, Mao L, Fang M. The laboratory tests and host immunity of COVID-19 patients with different severity of illness. JCI Insight. 2020;5(10).
43. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, Damoraki G, Gkavogianni T, Adami ME, Katsaounou P, Ntaganou M. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27(6):992–1000.
44. Barquera R, Collen E, Di D, Buhler S, Teixeira J, Llamas B, Nunes JM, Sanchez-Mazas A. Binding affinities of 438 HLA proteins to complete proteomes of seven pandemic viruses and distributions of strongest and weakest HLA peptide binders in populations worldwide. HLA. 2020;96(3):277–98.
45. Warren RL, Birol I. HLA predictions from the bronchoalveolar lavage fluid samples of five patients at the early stage of the Wuhan seafood market COVID-19 outbreak. ArXiv [Internet]. 2020;(class I):4–7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/32550246%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC7280900
46. Poulton K, Wright P, Hughes P, Savic S, Welberry Smith M, Guiver M, Morton M, van Dellen D, Tholouli E, Wynn R, Clark B. A role for human leucocyte antigens in the susceptibility to SARS-Cov-2 infection observed in transplant patients. Int J Immunogenet. 2020;47(4):324–8.
47. Vishnubhotla R, Sasikala M, Ketavarapu V, Reddy DN. High-resolution HLA genotyping identifies alleles associated with severe COVID-19: A preliminary study from India. Immunity Inflamm Dis. 2021;9(4):1781–5.
48. Poulton K, Wright P, Hughes P, Savic S, Welberry Smith M, Guiver M, Morton M, van Dellen D, Tholouli E, Wynn R, Clark B. A role for human leucocyte antigens in the susceptibility to SARS-Cov-2 infection observed in transplant patients. Int J Immunogenet. 2020;47(4): 324–8.
49. Gutiérrez-Bautista JF, Rodriguez-Nicolas A, Rosales-Castillo A, López-Ruz MÁ, Martín-Casares AM, Fernández-Rubiales A, Anderson P, Garrido F, Ruiz-Cabello F, López-Nevot MÁ. Study of HLA-A,-B,-C,-DRB1 and-DQB1 polymorphisms in COVID-19 patients. J Microbiol Immunol Infect. 2022;55(3):421–7.
50. Amoroso A, Magistroni P, Vespasiano F, Bella A, Bellino S, Puoti F, Alizzi S, Vaisitti T, Boros S, Grossi PA, Trapani S. HLA and AB0 polymorphisms may influence SARS-CoV-2 infection and COVID-19 severity. Transplantation. 2021;105(1):193–200.
51. Pisanti S, Deelen J, Gallina AM, Caputo M, Citro M, Abate M, Sacchi N, Vecchione C, Martinelli R. Correlation of the two most frequent HLA haplotypes in the Italian population to the differential regional incidence of COVID-19. J Transl Med. 2020;18(1):1–6.
52. Yung YL, Cheng CK, Chan HY, Xia JT, Lau KM, Wong RS, Wu AK, Chu RW, Wong AC, Chow EY, Yip SF. Association of HLA-B22 serotype with SARS-CoV-2 susceptibility in Hong Kong Chinese patients. HLA. 2021;97(2):127–32.
53. Wang W, Zhang W, Zhang J, He J, Zhu F. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). HLA. 2020;96(2):194–6.
54. Correale P, Mutti L, Pentimalli F, Baglio G, Saladino RE, Sileri P, Giordano A. HLA-B* 44 and C* 01 prevalence correlates with COVID-19 spreading across Italy. Int J Mol Sci. 2020;21(15):5205.
55. Littera R, Campagna M, Deidda S, Angioni G, Cipri S, Melis M, Firinu D, Santus S, Lai A, Porcella R, Lai S. Human leukocyte antigen complex and other immunogenetic and clinical factors influence susceptibility or protection to SARS-CoV-2 infection and severity of the disease course. The Sardinian experience. Front Immunol. 2020;11:605688.
56. Warren RL, Birol I. Retrospective in silico HLA predictions from COVID-19 patients reveal alleles associated with disease prognosis. medRxiv: The preprint server for health sciences. United States. 2020. doi: 10.1101/2020.10.27.20220863.
57. Schindler E, Dribus M, Duffy BF, Hock K, Farnsworth CW, Gragert L, Liu C. HLA genetic polymorphism in patients with coronavirus disease 2019 in Midwestern United States. HLA. 2021;98(4):370–9.
58. De Marco R, Faria TC, Mine KL, Cristelli M, Medina-Pestana JO, Tedesco-Silva H, Gerbase-DeLima M. HLA-A homozygosis is associated with susceptibility to COVID-19. HLA. 2021;98(2):122–31.

59. Ahmed SF, Quadeer AA, McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. Viruses. 2020;12(3).
60. Joshi A, Chandra B, Mannan MA ul, Kaushik V. Epitope based vaccine prediction for SARS-COV-2 by deploying immuno-informatics approach. Informatics Med Unlocked. 2020;19.
61. Liu G, Carter B, Gifford DK. Predicted cellular immunity population coverage gaps for SARS-CoV-2 subunit vaccines and their augmentation by compact peptide sets. Cell Syst. 2021;12(1):102–7.
62. Campbell KM, Steiner G, Wells DK, Ribas A, Kalbasi A. Prediction of SARS-CoV-2 epitopes across 9360 HLA class I alleles. BioRxiv. 2020;(310):0–11.
63. Silva-Arrieta S, Goulder PJR, Brander C. In silico veritas? Potential limitations for SARSCoV-2 vaccine development based on T-cell epitope prediction. PLoS Pathog. 2020; 16(6):2–6.
64. Sarkar B, Ullah A, Tuz F, Afrin M, Araf Y. Immunoinformatics-guided designing of epitope-based subunit vaccines against the SARS coronavirus-2 (SARS-CoV-2). Immunobiology. 2020;225.
65. Mukherjee S, Tworowski D, Detroja R, Mukherjee SB, Frenkel-Morgenstern M. Immunoinformatics and structural analysis for identification of immunodominant epitopes in SARS-CoV-2 as potential vaccine targets. Vaccines. 2020;8(2):1–17.
66. Marchan J. Conserved HLA binding peptides from five non-structural proteins of SARS- CoV-2—An in silico glance. Hum Immunol. 2020;81(10-11):588–95.
67. Albagi S, Mosab Yahya Al-Nour MY, Elhag M, Abdelihalim ATI, Haroun EM, Essa MEA, Abubaker M, Deka H, Ghosh A, Hassan MA. A multiple peptides vaccine against COVID-19 designed from the nucleocapsid phosphoprotein (N) and Spike Glycoprotein (S) via the immunoinformatics approach. Inform Med Unlocked. 2020;21:100476.
68. Muehling LM, Mai DT, Kwok WW, Heymann PW, Pomés A, Woodfolk JA. Circulating memory CD4 + T cells target conserved epitopes of rhinovirus capsid proteins and respond rapidly to experimental infection in humans. J Immunol. 2016;197(8):3214–24.