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Review Article

Human Leukocyte Antigen as a Predictor of COVID-19 Severity

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Abstract

Since the spread of the coronavirus disease 2019 (COVID-19) pandemic, many countries have been suffering from the disease, and patients exhibit an extensive spectrum of symptoms from mild to severe, and in some cases, it leads to death. Identifying vulnerability factors may help detect very high-risk subjects to prevent disease mortality. Since people have different human leukocyte antigen (HLA) alleles, and the frequency of the alleles varies between different races and geographic regions, it is inferred that there is an association between HLA and the vulnerability of the population. The present study aimed to find the most frequent HLA alleles that profoundly affect COVID-19 outcomes. To find the relevant articles, medical databases (Medline, PubMed, EMBASE, Cochrane Library, and the like) were searched by the keywords, and the results related to the association between HLA and COVID-19 morbidity were selected and briefly presented. Regarding the extracted information from several studies, HLA alleles with a strong affinity to COVID-19 epitopes such as HLA-A*11:01, HLA-A*02:06, and HLA-B*54:01 could result in mild symptoms, while those with weak affinity such as HLA-B*44:06 and HLA-B*46:01 contributed to severe symptoms and high mortality rate. Further, heterozygosity and frequency of HLA alleles could affect the disease outcome within populations. As a result, the vulnerability of the patients can be predicted through their HLA pattern, and preventive measures can be taken instantly for populations expressing high-risk alleles. HLA can be assumed as a global predictor of COVID-19 disease outcomes. High frequent alleles which affect the outcome of the disease are introduced as susceptibility-determining alleles.

Keywords: COVID-19, Human leukocyte antigen, SARS-CoV-2

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Background

Coronavirus often causes respiratory infection diseases ranging from the simple common cold to severe respiratory disorders such as Middle-East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). Coronavirus is originally zoonotic and affects the lower respiratory tract, engaging many vital organs (1-3). The severe acute respiratory syndrome coronavirus (SARS-COV-2) is another type of high contagious coronavirus which has emerged from Wuhan (China) in late 2019 (4-8). Soon after, the first coronavirus disease 2019 (COVID-19) case was reported in Wuhan, China. This infection rapidly spread throughout the world. Many research studies were conducted to find the reasons for different COVID-19 manifestations among the population (3). Human leukocyte antigen (HLA) loci which are considered the most polymorphic regions of the human genome can impact the progression of coronaviruses (9, 10), and in particular, may help distinguish individuals at higher risk for the disease. HLA gene is located on chromosome 6p21 and encodes cell surface molecules that present antigenic peptides to the T-cell receptor on T cells (11, 12). Pathogen peptides bind to peptide-binding specific regions in the distal extracellular end of HLA proteins. This binding region is known to have a very high diversity of amino acids as a result of the very high polymorphism of the exons encoding this part of the molecule (10, 13). Due to such considerable genetic diversity, molecules encoded by different HLA alleles manifest distinct physicochemical properties, leading to diverse classifications of HLAs. These properties provide different affinities to pathogen peptides and lead to either effective or ineffective presentation of the peptides. Therefore, the genetics of each person's HLA affects his/her immunological response to invading pathogens (14). Moreover, since HLA alleles have different frequencies all around the world, the affinity of HLA molecules to pathogen peptides varies based on region. As a result, it could be possible to predict the immunological reaction based on the geographic region (12, 13).

Objectives

In this study, after reviewing relevant works and evaluating different HLA alleles' affinity to their peptides, HLA alleles associated with mild or severe symptoms of the disease were presented based on the country. It is supposed that alleles with global distribution which are presented in more studies, either with high or low affinity, have more frequency in various societies; hence, they are better global predictors of disease symptoms, and they are also playing a more pronounced role in immunological reaction against the disease. Then, after presenting the results, alleles with higher frequency were introduced as determining alleles. Such alleles are useful for the recognition of more susceptible groups and regions and for developing vaccines with global efficacy.

HLA Alleles and Susceptibility to COVID-19

Studies on the association between HLA and the severity of infectious diseases date back to SARS disease studies which contributed to the COVID-19 pandemic. Lin et al evaluated the relationship between HLA class I and serious SARS infection in Taiwan. Their results illustrated that there is a direct and significant association between HLA-B*46:01 and severity of SARS pulmonary infection; that is, no severe infection was observed in the non-Taiwanese population who didn't have HLA-B*46:01 but expressed HLA-B*13:01 (9). Importantly, the frequency of HLA-B*46:01 was correlated with the susceptibility to SARS, and its frequency in western India and Wuhan, China, was 0.26% and 13.5%, respectively (15).

Despite considerable homology between the SARS-COV-2 sequence and SARS (16), it is better to do more investigations to find a significant correlation between HLA alleles and COVID-19 outcomes (17-19). Wang et al found that SARS-related susceptibility alleles did not necessarily occur in COVID-19 patients (20).

Role of HLA Allele Binding Affinity

The binding of coronavirus peptides to HLA class I in human populations was estimated elsewhere using an applied artificial neural network computer model. To this end, two haplotypes in human populations were defined for the expression of peptides in all nucleated cells and estimated viral peptides binding to these polymorphic molecules in human HLA. According to the results, HLA haplotypes with more affinity and stability and more extensive distribution resulted in severe immunological reactions to COVID-19 (13). Iturrieta-Zuazo et al evaluated the possible role of HLA class I genotype in COVID-19 disease and its progress. They conducted HLA typing (HLA class I) for 45 Spanish patients with mild to severe symptoms. Their results indicated that patients with mild symptoms had HLA molecules with higher theoretical affinity to Coronavirus peptides, and they were more heterozygote compared to patients with moderate to severe symptoms. They also noted that the difference in affinity of HLA to Coronavirus peptides is helpful for the determination of heterogeneity of clinical reaction to the disease and useful for the personal treatment of people based on the risk they may experience (21). Contrary to HLA-A class in which weakly binding alleles are rare, in class B, alleles such as HLA-B*46:01 (China and southwestern Asia) and HLA-B*52:01 (Japan, China, and India) have a relatively high frequency. Among the weakest class B alleles which were determined in this research, HLA-B*44:06, HLA-B*51:07, HLA-B*08:03, and HLA-B*46:01 can be noted. Regarding HLA-C class, it must be reminded that compared to the above classes, this HLA class has a lower affinity. The allele with the highest affinity in class C is HLA-C*03:02, and the weakest alleles are HLA-C*01:03, HLA-C*07:04, HLA-C*18:01, and HLA-C*18:02. In another study, it was determined that HLA-B*15:03 has a maximum affinity to the COVID-19 peptides; hence, it can be a protective allele against COVID-19 (22). As a result, it is expected that HLA typing can yield useful information about people's reactions to the disease and help us prioritize therapeutic options.

On the other hand, structural analysis of virus envelope proteins indicated that D416G S and ORFlab P4715L peptides as spike glycoproteins were important for the interaction of the virus with the ACE2 receptor and virus transmission. Spike glycoprotein had the most chance of mutation for adaptation of the virus to the new environment (23, 24). It can be concluded that D416G along with ORFlab P4715L is related to COVID-19 outcomes (25). High-affinity HLA alleles to these epitopes were investigated, and it was found that patients who expressed HLA alleles such as HLA-A*2:06, HLA-A*11:01, HLA-B*07:02, and HLA-B*54:01 with high binding affinity exhibited mild symptoms of disease (25).

Association of the HLA Alleles With Prevalence and Mortality of COVID-19

The relationship between genomic differences and COVID-19 mortality has been investigated in Japan. Researchers discovered that HLA-A*11:01 had a significant negative association with COVID-19 mortality. Furthermore, they showed that a similar trend can be observed between alleles HLA-A*02:06 and HLA-B*54:01 and disease mortality. Based on their results, the relationship between aforesaid alleles and prevalence of disease was negative and significant. As a result, they suggested that these alleles protected people against COVID-19 infection (25). In a study conducted in Italy, HLA-A*25, HLA-B*08, HLA-B*44, HLA-B*15:01, HLA-C*02, and HLA-C*03 demonstrated a positive correlation with COVID-19 infection, while HLA-B*14, HLA-B*18, and HLA-B*49 revealed a negative correlation with this viral infection (26). Correale et al demonstrated that the prevalence of COVID-19 could be affected by HLA alleles (27). Their results illustrated that for 1% increase in the frequency of HLA-B*44 and HLA-C*01,

the prevalence of COVID-19 could increase as much as 16% and 19%, respectively, implying the noticeable contribution of these two alleles to COVID-19 disease (27, 28).

Identifying COVID-19-associated HLA Class I and II Alleles

Table 1 summarizes the results of various studies regarding the high and low affinity of HLA classes I and II in many countries. Alleles on a global scale, especially those with a higher frequency between and within races, are reported. In this respect, the affinity of HLA class I alleles and the correlation of alleles with the severity of symptoms and mortality rate are reported among different ethnicities. It is clear that the presence of alleles with low affinity leads to severe symptoms with a higher mortality rate, while high-affinity alleles have weak symptoms and a low mortality rate. Since immune responses to viruses as intracellular pathogens are orchestrated through HLA class I presentation, most studies implemented HLA class I alleles. Limited studies indicated the correlation of HLA class II alleles with COVID-19 morbidity and mortality. Most of the high-affinity alleles of HLA class II are related to HLA-DR class, so their frequencies on a global scale are relatively high (29). Alleles with the weakest affinity in this class are HLA-DRB1*03:02 and HLA-DRB1*03:03. In HLA-DQ class, no strong affinity is observed, and alleles with the weakest affinity are HLA-DQA1*01:02, DQB1*04, and HLA-DQB*06:09 (22, 30-32)

Consideration of High-affinity HLA Alleles for Vaccine Design

Considering high-affinity HLA alleles with high global frequency for target peptides guarantees the success of the vaccine. An attempt for the development of the COVID-19 vaccine illustrated that among HLA-A, B, and C classes, HLA-A*02:01, HLA-A*01:01, HLA-B*40:01, and HLA-C*07:02 have the best binding to COVID-19 epitope (33). Abdelmageed et al used 10 MHC class I and II-bound peptides to develop an anti-COVID-19 vaccine. Based on their work, these 10 peptides were suitable candidates for vaccine design with 88.5 and 99.99% global coverage. Peptide vaccine based on T-cell epitope used envelope proteins as immunological targets (34). The selection of suitable peptides is another important issue. A study in Mexico revealed that HLA-A*02:03 has the highest affinity to GTHWFVTQR and FIAGLIAIV peptides of COVID-19 with the highest pathogenicity; as a result, they can be suitable epitopes for vaccine development (29).

HLA Alleles and COVID-19 Outcomes in the Iranian Population

In Iran, similar to the above studies, the results of Saadati et al illustrated that HLA-A*01, HLA-A*03, HLA-B*07, and HLA-B*38 are more frequent in patients who died of COVID-19 infection. In addition, despite the high frequency of HLA-A*02 and HLA-B*35 alleles in Iran, HLA-A*01 and HLA-B*07 are more dominant in mortality cases (35). Although this study just checked the HLA-A and B in a small group of dead patients infected with COVID-19, they compared their result with the result of a previously published study on HLA distribution among the normal Northeastern Iranian population (35). In a study on SARS, Yari et al analyzed the frequency of DR antigen in the Iranian population and suggested that HLA-DRB1*11, HLA-DRB1* 13, HLA-DRB1*15, and HLA-DRB1*04 have the highest frequency, respectively, while HLA-DRB1*09 has the lowest frequency in Iran (36). However, there is not enough published study on the relation between HLA class II and COVID-19 among the Iranian population. Regarding DR antigen, HLA-DRB1*11 and HLA-DRB1*13 alleles with the highest frequency and HLA-DRB1*09 allele with the lowest frequency in the Iranian population had a high affinity to SARS epitopes, thus resulting in mild symptoms of the disease (36). However, as mentioned before, SARS-related susceptibility alleles did not necessarily occur in COVID-19 patients (20). Hamidi Farahani et al evaluated the frequency of HLA alleles in 48 severe cases of COVID-19. Their results revealed that there is a significant association between HLA-B*38, HLA-A*68, HLA-A*24, and HLA-DRB1*01 and the severity of COVID-19 symptoms. Even though the HLA-DRB1*11 in this study represented higher frequency in patients, it did not show a significant association with the mortality rate of COVID-19 (37).

COVID-19 Severity Determining Alleles

Table 2 represents the alleles based on their highest frequency in different studies, their affinity to COVID-19 epitopes, the severity of disease, and fatality rate. It was assumed that if a certain allele appears more frequently in different papers, it can have a higher frequency in various societies; therefore, it can have a more pronounced effect on the immunological reaction of the patients. These alleles are introduced as determining alleles in what follows.

Conclusion

In conclusion, due to the central role of HLA molecules in host immune response, it is expected that resistance or susceptibility to COVID-19 depends on HLA alleles accordingly. Further, disease outcomes will become more predictable if we have the HLA pattern of patients. Affinity and heterozygosity of HLA alleles have a negative correlation with the severity of disease, and the frequency of alleles estimates the outcome of disease in the population. Therefore, it can be concluded that three important factors including affinity, heterozygosity, and frequency of HLA alleles affect COVID-19 outcomes. Based on the affinity and frequency, the most important alleles

Table 1. HLA Class I and II Alleles Based on Their Affinity to Peptides and Correlation With Morbidity and Mortality Rate in Different Countries

HLA Allele	Possible Epitope	Epitope Affinity[a]	Symptom Severity[b]	Mortality Rate[c]	Ethnicity	Ref.
HLA-A*11:01	S416G/ ORFab 4715L	Strong	Mild	Low	Japan	(25, 38)
HLA-A*02:06	S416G/ ORFab 4715L	Strong	Mild	Low	Japan	(25, 30, 39)
HLA-B*54:01	S416G/ ORFab 4715L	Strong	Mild	Low	Japan	(25)
HLA-A*25		Weak	Severe	High	Italy	(27)
HLA-B*08:03	YLQPRTFLL /267-275	Weak	Severe	High	Italy	(27)
HLA-B*44:06		Weak	Severe	High	Italy	(27, 30)
HLA-B*15:01		Weak	Severe	High	Italy	(27)
HLA-C*02		Weak	Severe	High	Italy	(27)
HLA-C*03		Weak	Severe	High	Italy	(27)
HLA-B*14		Strong	Mild	Low	Italy	(27)
HLA-B*18		Strong	Mild	Low	Italy	(27)
HLA-B*49		Strong	Mild	Low	Italy	(27)
HLA-B*13:01		Strong	Mild	Low	Taiwan	(11)
HLA-B*46:01		Weak	Severe	High	Italy	(9, 22, 30, 40)
HLA-A*02:03	FIAGLIAIV	Strong	Mild	Low	Mexico	(29, 30)
HLA-DPA*01:03		Strong	Mild	Low	Mexico	(29)
HLA-DPB1*02:01		Strong	Mild	Low	Mexico	(29)
HLA-DPA1*02:01		Strong	Mild	Low	Mexico	(29)
HLA-DPB1*01:01		Strong	Mild	Low	Mexico	(29)
HLA-DPA1*03:01		Strong	Mild	Low	Mexico	(29)
HLA-DPB1*04:02		Strong	Mild	Low	Mexico	(29)
HLA-DQA1*05:01		Strong	Mild	Low	Mexico	(29)
HLA-DQB1*03:01	VVVLSFELL	Strong	Mild	Low	Mexico	(29)
HLA-DRB1*01:01	FELLHAPAT	Strong	Mild	Low	Mexico	(29, 30)
HLA-DRB1*09:01	FGAGAALQI	Strong	Mild	Low	Mexico	(29)
HLA-DRB1*07:01	FTISVTTEI	Strong	Mild	Low	Mexico	(29)
HLA-A*02:11	VVFLHVTYV /1057-1065	Strong	Mild	Low	Global	(30)
HLA-A*02:22		Strong	Mild	Low	Global	(30)
HLA-A*02:12		Strong	Mild	Low	Global	(30)
HLA-A*02:02		Strong	Mild	Low	Global	(30)
HLA-A*02:01	YLQPRTFLL /267-275	Strong	Mild	Low	Global	(30, 33, 39)
HLA-A*02:05		Strong	Mild	Low	Global	(30)
HLA-A*02:35		Strong	Mild	Low	Global	(30)
HLA-A*02:40		Strong	Mild	Low	Global	(30)
HLA-A*02:24		Strong	Mild	Low	Global	(30)
HLA-A*02:09		Strong	Mild	Low	Global	(30)
HLA-B*15:03		Strong	Mild	Low	Global	(22, 30)
HLA-B*35:10	SANNCTFEY /160-168	Strong	Mild	Low	Global	(30)
HLA-B*15:17		Strong	Mild	Low	Global	(30)
HLA-B*15:25		Strong	Mild	Low	Global	(30)
HLA-B*15:39		Strong	Mild	Low	Global	(30)
HLA-B*52:01		Weak	Severe	High	Global	(30, 39)
HLA-B*51:07		Weak	Severe	High	Global	(30)
HLA-C*03:02		Strong	Mild	Low	Global	(30)
HLA-C*01:03		Weak	Severe	High	Global	(30)
HLA-C*07:04		Weak	Severe	High	Global	(30)
HLA-C*18:01		Weak	Severe	High	Global	(30)

Table 1. Continued

HLA Allele	Possible Epitope	Epitope Affinity[a]	Symptom Severity[b]	Mortality Rate[c]	Ethnicity	Ref.
HLA-C*18:02		Weak	Severe	High	Global	(30)
HLA-DRB1*01:04		Strong	Mild	Low	Global	(30)
HLA-DRB1*11:02		Strong	Mild	Low	Global	(30)
HLA-DRB1*13:01		Strong	Mild	Low	Global	(30)
HLA-DRB1*13:22		Strong	Mild	Low	Global	(30)
HLA-DRB1*03:02		Weak	Severe	High	Global	(30)
HLA-DRB1*03:03		Weak	Severe	High	Global	(30)
HLA-DQ1*01:02		Weak	Severe	High	Global	(30)
HLA-DQ1*06:09		Weak	Severe	High	Global	(30)
HLA-B*51:01		Weak	Severe	High	China	(31)
HLA-C*14:02		Weak	Severe	High	China	(31)
HLA-B*08:01	YLQPRTFLL /267-275	Weak	Severe	High	Taiwan	(27)
HLA-A*01:01	WTAGAAAYY /256-264	Strong	Mild	Low	China	(33)
HLA-B*40:01		Strong	Mild	Low	China	(33)
HLA-C*07:02		Strong	Mild	Low	China	(33)
HLA-A*01		Weak	Severe	High	Iran	(35)
HLA-B*03		Weak	Severe	High	Iran	(35)
HLA-B*07		Weak	Severe	High	Iran	(35)
HLA-B*35		Weak	Severe	High	Iran	(35)
HLA-A*24		Weak	Severe	High	Iran	(37)
HLA-B*38		Weak	Severe	High	Iran	(37)
HLA-B*68		Weak	Severe	High	Iran	(37)
HLA-DRB1*01		Weak	Severe	High	Iran	(37)
HLA-A*24:02	YLQPRTFLL /267-275	Strong	Mild	Low	Japan	(28, 38, 39)
HLA-C*01:02		Strong	Mild	Low	Japan	(39)
HLA-C*08:01		Strong	Mild	Low	Japan	(39)
HLA-C*12:02		Strong	Mild	Low	Japan	(39)
HLA-DRB*08		Weak	Severe	High	Italy	(40)
HLA-A*25:01		Weak	Severe	High	Italy	(27)
HLA-B*15:01		Weak	Severe	High	Italy	(27)
HLA-B*51		Weak	Severe	High	Italy	(27)
HLA-C*01		Weak	Severe	High	Spain	(32)
HLA-A*32	YLQPRTFLL /267-275	Strong	Mild	Low	Spain	(32)
HLA-B*39		Weak	Severe	High	Spain	(32)
HLA-C*16		Weak	Severe	High	Spain	(32)
HLA-A*11	GTHWFVTQR /1096-1104	Weak	Severe	High	Spain	(32)
HLA-DQB1*04		Weak	Severe	High	Spain	(32)

Note. HLA: Human leukocyte antigen; Ref.: Reference; COVID-19: Coronavirus disease 2019.
[a] Epitopes affinity (strong/weak) are presented based on references. Binding affinity predictions can be obtained using the allele frequency database (41-43). [b] Symptom has been classified (mild/severe) based on CDC guidelines (44). [c] COVID-19 high mortality rate is about (10-30%) of all cases (45).

were introduced as susceptibility-determining alleles in Table 2. Such information is useful for the development of customized treatment and vaccine design according to the genetics of the human population. Accordingly, the production of vaccines based on the dominant and high-affinity HLA alleles to COVID-19 epitopes can decrease the mortality rate and the transmission chain of the virus.

Authors' Contribution
Study concept and design: NKH. Drafting of the manuscript: AJ and NKH. Critical revision of the manuscript for important intellectual content: AS and NKH.

Conflict of Interests
The authors declare that they have no conflict of interest.

Ethical approval
Not applicable.

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Table 2. High Global Frequent Alleles as Determining Alleles Based on Affinity, Severity of disease, and Mortality Rate

HLA Allele	Epitope Affinity[a]	Symptom Severity[b]	Mortality Rate[c]
HLA-B*46:01	Weak	Severe	High
HLA-B*44:06	Weak	Severe	High
HLA-B*52:01	Weak	Severe	High
HLA-B*08:01	Weak	Severe	High
HLA-A*02:06	Strong	Mild	Low
HLA-A*02:01	Strong	Mild	Low
HLA-B*15:03	Strong	Mild	Low
HLA-A*24:02	Strong	Mild	Low
HLA-A*02:03	Strong	Mild	Low
HLA-DRB1*01:01	Strong	Mild	Low

Note. HLA: Human leukocyte antigen; COVID-19: Coronavirus disease 2019.

[a] Epitopes Affinity (strong/weak) are presented based on references. Binding affinity predictions can be obtained using the allele frequency database (41-43). [b] Symptom has been classified (mild/severe) based on CDC guidelines (44). [c] COVID-19 high mortality rate is about (10-30%) of all cases (45).

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