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Review Article

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Gene Polymorphisms and Their Association to Coronavirus Family Infections: Susceptibility in Different Populations

Souad Mahmoud AL-OKLA

Associate professor of Immunology, Department of Biochemistry, College of Medicine and Health Sciences, National University of Science and Technology, Sohar, Sultanate of Oman

***Corresponding author**
Souad Al-Okla, Associate professor of Immunology, Department of Biochemistry, College of Medicine and Health Sciences, National University of Science and Technology, Sohar, Sultanate of Oman, P.O.Box:391, Postal Code: 321, Al Tareef, Sohar, Sultanate of Oman

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Abstract

Human leukocyte antigen (HLA) loci are highly polymorphic and determine differential features of the immune response in subjects from different regions. HLA genes have been proposed to determine genetic susceptibility to several diseases, particularly to viral infections. Moreover, it has been suggested that each ethnic group could have a different specificity of T-lymphocyte reactivity to the same viral infections. In this review, we analyzed the distribution of HLA types in countries of the Asian, European and North African region. Also, we studied the relation between these HLA polymorphisms and susceptibility to infection by the coronavirus. Our findings indicated that homozygosity would increase susceptibility to viral infections and, in some cases, to coronavirus infection. HLA types showing higher susceptibility were reported in Asian population, including China, Singapore, and Taiwan. In contrast, lower susceptibility HLA variants were detected among African populations, some Asian populations, and Mediterranean populations. The presented evidence along with the spread pattern of COVID-19 infection suggests that HLA genetic variants might be related to its infection susceptibility and severity. The investigation of HLA genetic variants distribution would be a useful tool to predict different populations' susceptibility to viral infections.

Keywords: Human leukocyte antigen, COVID-19, T-lymphocyte, SARS, ACE2

Introduction

Classical human leukocyte antigen (HLA) loci are located in the major histocompatibility complex, on chromosome 6. The HLA loci include class I molecules (HLA-A, -B, -C, -E, -F, and –G), class II (HLA-DR, -DQ, -DM, and –DP), and class III. The high complexity of HLA molecule types have led to nomenclature systems that contemplate serological phenotyping and DNA genotyping. However, even these classifications do not discriminate well between alleles [1].

It has been described that class I HLA molecules are expressed on most cells and present antigens to CD8+ T cells. Class I HLA molecules are comprised of 2 subunits (α chain and β2-microglobulin). It is known that α subunit is highly polymorphic. On the other hand, class II HLA molecules include an α chain and a β chain where mainly the α chains of HLA-DQ and HLA-DP and β chains are highly polymorphic (1). According to the IPD-IMGT/HLA database2 (Release 3.34.0 on Oct-18 2018), it has been shown that of 8 major HLA genes (HLA-A, -B, -C, -DRB1, -DPA1, -DPB1, -DQA1, and -DQB1) over 16,000 alleles have been described, which encode for more than 13,000 protein variants. In addition, populations like African, European, Chinese, and Japanese have shown different expression patterns, suggesting that HLA polymorphisms might determine differential features of the immune response between subjects from different regions [2].

HLA Gene Polymorphism and the Genetic Susceptibility to Infectious Diseases

HLA genes have been proposed for genetic susceptibility to several diseases [1]. In the recent years, many studies have indicated that HLA types might be related to susceptibility to viral infections. Blackwell et al. have suggested that the associations between classical class I and class II HLA alleles and infectious diseases have been better demonstrated for chronic viral infections, which will be the focus of our study [2].

HLA homozygosity has been related to a higher susceptibility to infections in genetically isolated populations.Different types of

HLA have been significantly correlated with geographical distribution, as well as those allelic variants differentiate ethnic groups. So, each ethnic group could have different specificity of T-lymphocyte reactivity to the same viral infections [3].

HLA-A2, B51, and DRB1*16 alleles reported frequencies were compared among Oman, Saudi Arabia, Iran, Kenya, Jordan, United Arab Emirates, and Pakistan [4]. It was observed that HLA-B51 showed the higher frequency among Saudis and Emiratis. HLA-DRB1*16 frequency was highest in Omani, Emiratis and Pakistani population. On the other hand, the lowest frequency of HLA-DRB*16 was observed in Kenya and Jordan followed by Saudi Arabia and Iran.

In other studies from different countries, it was reported that the most frequent HLA type was DQB1*06 in Saudi Arabia (26%), while DQ4 was the most frequent in Iran (15.2%), and DQ3 was the most common in East Africa (21.8%) [5]. HLA-DQB1*05 was found to be highly frequent in Malaysia (37.1%) and in Pakistan (Baloch) (34%) [6]. The HLA-DQB1*02 is a common allele. Another study reported the frequency of this allele in different countries, such as France (24%), Libyan Jews (33.3%), Morocco (30.6%), Spain (48%), and Turkey (23.8%) [6].

Furthermore, an earlier study performed with 126 healthy Omanis blood donors from all regions of the country showed that HLA-DR2 was the most frequent allele in the Omani population and that its frequency was much higher than the ones reported in Saudi Arabia and Kuwait [7].

In a meta-analysis study, the HLA distribution in North African and Oriental Arab populations was analyzed and then compared to neighbouring populations. The results showed a genetic relationship between Bahrainis, Emiratis, and Omanis. These populations are similar to Pakistanis, Indians, Iranian Arabs (Famoori), Sardinians, Egyptians, and some sub-Saharan Africans, and were related to Eastern Mediterranean populations [8].

A study carried out in the Spanish population revealed a relatively high homogeneity in HLA types and frequencies. HLA-B presented the higher diversity. HLA-C*04:01 was the only HLA-C variant observed while HLA-DQA1*05:01 was the only HLA-DQ type described [9]. Among Italian population, an analysis performed on 120,926 bone marrow donors indicated that the three most frequent Italian haplotypes were HLA - A*01:01,B*08:01, C*07:01, DRB1*03:01 (2.5%), A*02:01, B*18:01, C*07:01, DRB1*11:04 (1.1%), and A*30:01,B*13:02,C*06:02,DRB1*07:01 (1.1%) [10]. Another study with 246 Greek healthy donors indicated that the most frequent HLA types were HLA-A*02 (44.3%), HLA-A*24 (27.2%), HLA-B*51 (28.5%), HLA-B*18 (26.8%) and HLA-B*35 (26.4%) and HLA-Cw*04 (30.1%) and HLA-Cw*12 (26.8%). The most frequent MHC class II alleles were HLA-DRB1*1104 (34.1%), HLA-DQB1*0301 (54.5%) and HLA-DPB1*0401 (59.8%) [11].

HLA haplotypes A1-B8–DR3 and A29-B44-DR7 are common European haplotypes which have been associated to the Mediterranean population. The study of HLA genetic variants Mediterranean population suggests that there are relations with sub-Saharan populations. HLA genomic analysis revealed that Greeks would be significantly related to Saharan Africans while Kurds and Armenians would be genetically related to Turks and other Middle East populations. Also, Iberians would be genetically connected to North African Berbers. Sub-Saharan groups would share DRB1 alleles with Greeks (DRB1*0305, *0307, *0411, *0413, *0416, *0417, *0420, *1112, *1120, *1304, *1310) [12].

Coronavirus

Coronavirus cause a mild respiratory pathology that can become severe in immunocompromised patients. This emergent virus is a serious threat. In the past two decades, coronavirus caused severe acute respiratory syndrome (SARS-CoV) and Middle East respiratory syndrome (MERS-CoV) in China, and recently a new threat has been raised with COVID-19. The zoonotic transmission is very common. This kind of viruses attach to the cell surface by firstly binding to glycans such as sialic acids or heparan sulphate and then interacting with an entry receptor. It has been suggested that coronavirus entry receptors could be angiotensin-converting enzyme2 (ACE2) and dipeptidyl peptidase 4 for SARS and MERS, respectively. Binding to ACE2 would involve S-protein of SARS-CoV, suggesting that ACE2 variants could reduce this association (Figure 1) [13].

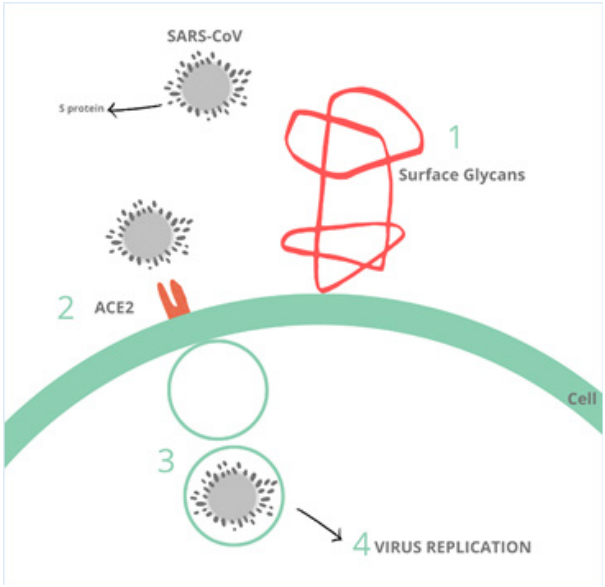

Figure 1: SARS-CoV entry to the human cell. The virus interacts with cell surface glycans (1), binds to ACE2 entry receptor (2) and becomes internalized (3). Inside the cell the virus releases its nucleic acids and replicates using the cell machinery (4).

On the other hand, ACE gene polymorphisms have been associated with population geographic distribution.Previous studies showed that Asian males may have higher expression levels of ACE2, but there is limited information regarding other populations. In addition, it has been found that the ACE2 SNP rs2285666 allele frequency would be higher in the Chinese population respect to other populations such as American, European or African population. Moreover, it was shown that the homozygous mutation rate was higher in males than in females in the Chinese population [14]. In a recent study, it was proposed that ACE2 could be the receptor

for coronavirus 2019-nCoV/SARS-CoV-2 and that its expression levels/patterns might affect susceptibility to COVID-2019 infection. However, no mutations were found in the residues involved in coronavirus binding in the analyzed populations (databases from China, Europe, Asia, Africa, and America), suggesting that there would not exist a natural resistance for Coronavirus [14]. Similarly, a study by Chiu et al. concluded that there was no association between ACE2 genetic variants and SARS susceptibility or outcome [14]. On the other hand, Fang et al. hypothesized that an increased expression of ACE2 would facilitate the infection with COVID-19 [15]. Since diabetes and hypertension treatment include the use of ACE2-stimulating drugs, the authors proposed that patients with these diseases would present a higher risk of COVID-19 infection. It should be considered that there are no data providing evidence of the effects of anti-hypertensive medications in hypertensive COVID-19 infected patients and current guidelines advise continuing regular therapy [16].

Human leukocyte antigen class I receptor has been proposed as Human coronaviruses (HCoV) OC43, and HKU1 receptor, but these findings were not confirmed in subsequent studies. In a study by Szczepanski performed in 2019 it was found that bovine coronavirus and canine coronavirus use HLA-I as receptor [17]. In another study performed in 2008 by Chan, it was shown that HCoV-HKU1 S required HLA-C as receptor to enter the cell. Also, it was demonstrated that the virus was able to infect cells without HLA-C expression in a lower percentage, suggesting that HLA-C would be important but not the sole receptor for cell entry [18].

HLA Types Association with Coronavirus Infection Susceptibility and Severity

According to the latest report of the World Health Organization, novel coronavirus infection (COVID-19) is affecting over 1 million people worldwide. Countries like China, Korea, United States, Spain, Germany, Italy, France, the United Kingdom, Turkey, and Iran have shown the highest infection and mortality rates [19].

Many factors can influence COVID-19 presentation and progression such as demographics, sociological interactions, medical access, immune proteins variants (including HLA), past immunity to other coronavirus, and mutations in SARS-CoV-2 (20).The geographical and ethnical spread pattern of coronavirus has led to suggest that genetic variant may affect the clinical course and the susceptibility of coronavirus infection. The study of the association between HLA types and susceptibility to coronavirus infection and severity of presentation has raised interest in the scientific community. In Italy, the number of COVID-19 case fatalities has been much higher than in China even though the number of diagnosed cases was high in both countries. Over 10,000 deaths have been registered in Italy, while China informed 3,340 deaths, and the number of cases was 132,000 and 83,000, respectively, leading to case fatality rates of 12.4% and 4.1% (Table 1) [20]. Similarly, in Spain 135,000 cases have been reported with a case fatality rate of 9.6%. On the other hand, United States and Germany reported many cases (123,000 and 52,000 cases respectively) but presented lower case fatality rates (1.8% and 1.6%) [20]. Moreover, Oman has reported almost1, 790 COVID-19 cases and 9 deaths since February of 2020 [21]. The most frequent haplotypes described in Oman are A*01:01-B*08:01-C*07:01-DRB1*03:01 (frequency of 5.7%) [22].

Table 1: HLA types and mortality rates among the countries with a higher number of cases

Country	N° of cases	Case fatality rates	Most frequent HLA haplotypes (frequency)
China	83071	4.1%	DRB1*14:01:01-DQB1*05:02:01 (63.3%)
Spain	135032	9.6%	DPA1*01:03-DPB1*04:01 (30%)
Italy	132547	12.4%	DRB1*03:01-DQB1*02:01 (49.2%)
Germany	99225	1.6%	DRB1*15:01-DQB1*06:02 (25.3%)
United states	333811	2.9%	B*40:02-C*03:04 (27.2%)

To the best of our knowledge, there are few recent studies that show associations between COVID-19 and HLA types in the countries that present the higher number of cases. However, a number of earlier studies indicated an increased frequency of certain HLA types in patients infected with SARS and MERS coronavirus. Previous studies indicate that populations from South East of Asia would be more susceptible to SARS infection [23].

Nguyen et al., were able to analyze the relationship between the genetic variability among HLA-A, B, and C and susceptibility/severity of COVID-19 infection [24]. The study was carried out by in silico analysis of binding affinity between HLA genotypes and viral peptides. The authors found that HLA-B*46:01 presented the lowest affinity binding for COVID-19 peptides, leading to a low T-cell mediated antiviral response and a consequent higher susceptibility among individuals presenting this allele.HLA-B*46:01 allele is highly frequent in Asian population, including China, Singapore, and Taiwan [25]. Moreover, they showed that HLA-B*15:03 would be related to higher protection against coronavirus infection and presents higher frequency among genetically derived African populations. According to a previous study, Zulu ethnic group showed the highest frequency of HLA-B*15:03. This population is mainly located in southern Africa [26]. African countries have reported few COVID-19 cases respect to other continents so far [21].

A study carried out in Hong Kong was able to relate SARS individuals with HLA-B*07:03 and HLA-DR*03:01. The first allele was found to increase susceptibility to the infection while the second allele conferred resistance factors to the infection [27]. Furthermore, a Taiwanese study found that patients with HLA-Cw*15:02 and HLA-DR*03:01 alleles were linked to an increased SARS infection resistance [28]. This suggested that HLA-DR*03:01 might enhance the function of CD4+ T helper cells. Among the class I HLA genes, HLA-B was associated with protective roles against

other viral infections.Interestingly, HLA-DRB1*03:01 is one of the most frequent haplotypes in Italian and Oman populations [22].

Chen et al., suggested that HLA-Cw*0801 would be associated with SARS-CoV infection susceptibility and they observed that homozygosity for this allele led to a higher risk of infection [29]. However, the presence of the mentioned allele was not related to disease severity. In agreement with Nguyen et al., a study by Lin et al. showed that HLA-B 4601 was associated with increased severity of SARS infection in Asia population [23, 24]. These results were confirmed in another study by Chen et al [29]. Conversely, a study by Wang et al. indicated that the prevalence of HLA-B 4601 in SARS cases was almost the same as in controls group [28]. Additionally, Chen et al. study showed that HLA-Cw 1502 was associated with a lower susceptibility to SARS infection.

The HLA alleles present in Oman and other populations that have been described in the previous section have been searched through literature in relation to coronavirus infection susceptibility. Interestingly, Hajeer et al., revealed that HLA-DRB1*02:02 might be related to an increased susceptibility to MERS, and HLA-DQB1*02 has been shown to be highly frequent in France, Spain, and Turkey which have presented a high number of COVID-19 infected patients [19, 30]. Additionally, HLA-DRB1*03 has been shown to be common in Omanis, Southeast Asia, and Mediterranean populations, which, as reported above, has been associated to an increased resistance to the virus.

Conclusions

The body of evidence indicates that genetic variations, especially in HLA genes, influence individuals' immune response towards viruses.The spread pattern of COVID-19 infection suggests that HLA genetic variants might be related to its infection susceptibility and severity. Few studies have been led so far, but recent investigations that revealed associations between COVID-19 infection and HLA types might trigger new studies that could be helpful to predict coronavirus spread behaviour and for countries to be prepared. Additionally, understanding possible HLA variations in relation to COVID-19 progress could help recognize high-risk individuals. Since HLA typing is fast and inexpensive, HLA typing could be used in addition to COVID-19 testing in order to identify patients with potential worse prognosis and even prioritize them for an eventual vaccination program.

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