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Associations between HLA Allele frequencies and the development and/or severity of COVID-19

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COVID-19 is a respiratory disease caused by a novel coronavirus and is an ongoing global pandemic. Only limited studies have reported HLA gene, most of which are *in silico* and a few cases control studies from Hong Kong, China, Taiwan, Vietnam and United Kingdom. The aim of this study was to find the association of HLA polymorphisms with incidence and severity of COVID-19, we focused on 3 major genes of HLA which are HLA-A, -B, -C, and the common variant alleles-DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1. Recent published articles reporting the HLA alleles in COVID-19 patients were included. Frequency of HLA alleles in general population was obtained from allele databases already available. Recent reported alleles were compared to the allele frequency in databases to deduce the associations. DRB1* 07.01 was most commonly reported in China, Hong Kong and UK. B*15 and DQB1*06.01 most frequent in China Hong Kong, Vietnam. B*13.01, DRB1*12.02, DQA1*01.01 and DPB1*03.1 were significantly associated with disease severity. Genetic diversity of different populations and polymorphisms in HLA alleles may have an association and role in the COVID-19 infection. Very few studies have been reported on HLA typing in COVID-19 patients and these studies are reported from China, Hong Kong, Vietnam which are pure breeds. More researchers in other heterogenic populations are required to establish a confirmed association.

Keywords: HLA, MHC, COVID-19, Human leukocyte antigen, Major histocompatibility complex

INTRODUCTION

In late December 2019, a different type of respiratory infection (atypical pneumonia) broke out with an unknown cause, in Wuhan, China (Wu et al. 2020a; Wu et al. 2020b). Severe acute respiratory syndrome-Corona Virus-2 (SARS-CoV-2) was subsequently identified as the causal agent of patients' respiratory epithelium-related pneumonia (Xu et al. 2020). The World Health Organization (WHO) first designated the newly found virus as 2019-nCoV. It is a novel coronavirus that belongs to a new evolutionary branch within the CoV. Later, on February 11, 2020, the International Committee of Viruses changed the new coronavirus's designation from "2019-nCoV" to "SARS-CoV-2" (Gorbalenya et al. 2020). The SARS-CoV-2 sickness was referred to as "coronavirus disease 2019" (COVID-19) (WHO, 2020). Coronaviruses, a wide family of enveloped positive stranded RNA viruses, including the Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) and the severe acute respiratory syndrome coronavirus (SARS-CoV), cause respiratory diseases ranging from a mild common cold to serious respiratory failure. The SARS-CoV-2 virus is the seventh member of its family to be discovered (Zhu et al. 2020). Not all of the infected individuals had the same symptoms; over 80% had moderate symptoms similar to those seen in previous cases of SARS-CoV and MERS-CoV (Denison, 2004; Lau et al. 2004).

As airborne human-to-human transmission has been identified as the mode of transmission for COVID-19, infected individuals often distribute virus particles anytime

they speak, breathe, cough, or sneeze (Cucinotta and Vanelli, 2020). The COVID-19 outbreak in China was deemed a Public Health Emergency of International Concern by the WHO on January 30, 2020, and the danger was higher for nations with weak health systems. Early identification, isolation, and rapid treatment were said to have the potential to stop the spread of the disease (Zhu *et al.* 2020). The COVID-19 outbreak was deemed a worldwide emergency due to the 13-fold increase in cases outside of China, the three-fold increase in the number of countries with cases, and the anticipated growth in disease propagation.

Patients usually present with flu like symptoms, fever, cough and loss of smell or taste with or without dyspnea. In proportion of persons sometimes, condition worsens and leads to progressive viral pneumonia and acute respiratory distress syndrome (Denison, 2004; Cucinotta and Vanelli, 2020). Both epidemiological and clinical features of patients with COVID-19 demonstrate that the infection with SARS-CoV-2 can cause clinical presentation with clusters of severe respiratory illness greatly resembling the disease caused by SARS-CoV, leading to requirement of mechanical ventilation of patients in intensive care unit (ICU) and subsequently higher mortality (Cucinotta and Vanelli, 2020). As reported from China, a larger case-series of >70,000 participants 81% of cases were mild, 14% were in need of hospitalization, with 5% requiring intensive care and 2.3% was proportional mortality. Elderly individuals are particularly at risk (Huang *et al.* 2020; Morawska and Cao, 2020). To deal with this unique health issue the scientists are trying to attain maximum understanding of the mechanism SARS-CoV-2 contaminates, the genetic & non-genetic susceptibility factors that influence our protection against the consequences (Chen et al. 2020).

Since HLA plays a key role in the immune response of humans to pathogens. It has been hypothesized that the diversity seen in most polymorphic gene of HLA in different populations may have some association with the occurrence, susceptibility and presentation of COVID-19 (Bhatraju et al. 2020). The Human Leukocyte Antigen (HLA) system with its alleles has a pivotal genetic role in viral antigen presentation pathway determining the outcome of many viral diseases which confers difference in viral susceptibility and severity of disease. It has been studied that disease caused by the closely related SARS-CoV presented more severely among individuals with the genotype of HLA-B*46:01 genotype (Gorbalenya et al. 2020; Denison, 2004; Lau et al. 2004). Associations between viral diseases and HLA genotype is also seen in other unrelated viruses like hepatitis, severe acute respiratory syndrome (SARS) and human immunodeficiency virus 1 (HIV-1) as well (Chour *et al.* 2020; Sanchez-Mazas, 2020; Wang et al. 2020). For example, patients infected with HIV, found to have association of HLA-A*0202 and HLA A*6802 with a significantly decreased rate of HIV-1 seroconversion (Lau et al. 2004). While the clinical picture of COVID-19 pandemic continues to emerge, the immune response against SARS-CoV-2 predicts the role of individual genetic variability and leaves with substantial unanswered questions (Gorbalenya et al. 2020).

A comprehensive in silico analysis of binding affinity of viral peptide of entire SARS-Cov-2 and major histocompatibility complex (MHC) class I across 145 different HLA types, reported that variation in HLA affects the course of COVID-19. Individuals at higher risk from the disease can be identified easily with the help of the knowledge of genetic variability. Assessment of severity of viral disease can be improved with HLA typing paired with COVID-19 testing (Sanchez-Mazas, 2020). Several collaborative and large efforts to generate, analyze and share genetic data are currently underway to understand the links between susceptibility of COVID-19 and human genetic variation. COVID-19 Host Genetics Initiative (COVID19hg.org) is the most prominent amongst them. Mostly these studies are supported by the observations made after the outbreak of SARS–CoV-1 in 2003 (Gao *et al.* 2020). Associations between the occurrence, progression and /or severity of SARS and HLAs is found in few populations. HLA-B*07:03, B*46:01, DRB1* 03:01, DRB1*12:02 alleles have been reported to be associated with susceptibility to SARS (Vabret *et al.* 2020). HLA-B* 4601 found to be associated with the severity of SARS in south Asian population. The objective of this study was to find the association of HLA polymorphisms with incidence and severity of COVID-19, we focused on 3 major genes of HLA which are HLA-A, -B, -C, and the common variant alleles-DRB1, -DRB3/4/5, -DQA1, -DQB1, -DPA1, and -DPB1.

MATERIALS AND METHODS

Population density in different countries and the statistics of COVID-19 cases (disease incidence, severity, mortality) was obtained from World Health Organization database. The purpose was to assess the densities of populations and the incidence to observe the genetic association of disease. The studies reporting the frequency of HLA alleles in COVID-19 patients were included. Few studies were conducted in China, Taiwan, Hong Kong, Vietnam and United Kingdom. Later, these frequencies were compared with the frequencies of these alleles in those general populations as mentioned in the databases of Compare Global HLA allele frequencies (http://igdawg.org/software/browser-beta.html) and Allele frequency Net Database (http://www.allelefrequencies.net/pop6001a_gsb.asp). Statistical analysis was done by using SPSS version 24.

RESULTS

Figure 1 shows that India and China are high density populations and the percentages of COVID-19 patients in India was very low as compared to China. USA population density was low but the percentages of COVID-19 patients

were very high. Japan has highes ratio of cases as well.

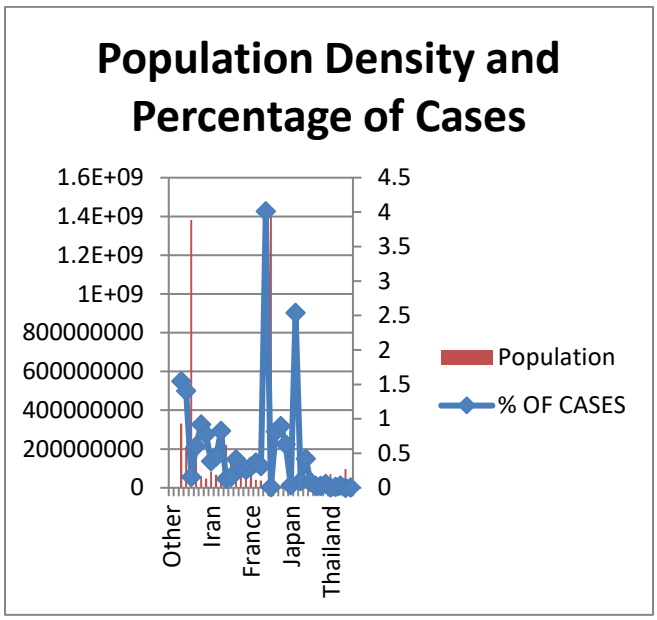

Figure 1: Population Density and percentages of cases worldwide

Figure 2 depicts that population density and percentage of deaths vary from population to population. India and china were high density population but the death rate in India was low as compared to China.

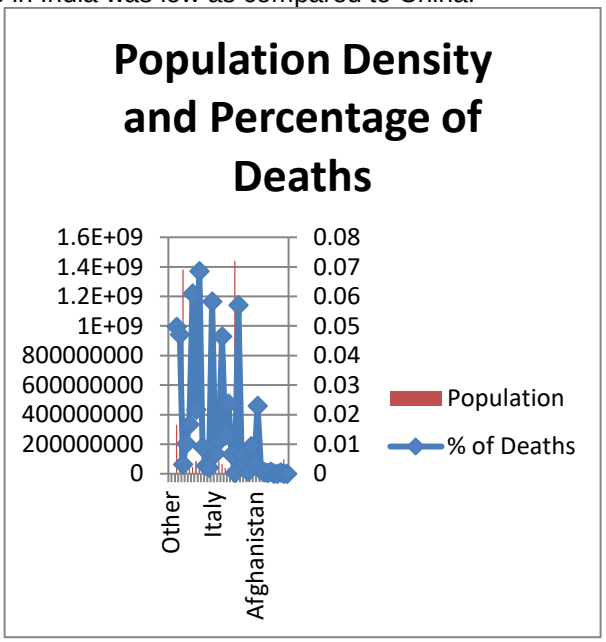

Figure 2: Population Density and Percentages of deaths worldwide

HLA- DRB1*07:01 was most frequent in China, UK and Hong Kong (Figure 3A). HLA-B*15 was frequent in China, Vietnam and Hong Kong and HLA-DQB1*06:01 was most frequent in China, Vietnam and Hong Kong (Figure 3B). HLA-b*13:01 was most frequent in China then in Hong Kong and Taiwan, HLA-DRB1*12:02 was most frequent in China than in Hong Kong and Taiwan, HLA-DQA1*01:01 was most frequent in Hong Kong, then China and Taiwan and HLA-DPB1*03:01 was most frequent in China than Taiwan and Hong Kong (Figure 3C).

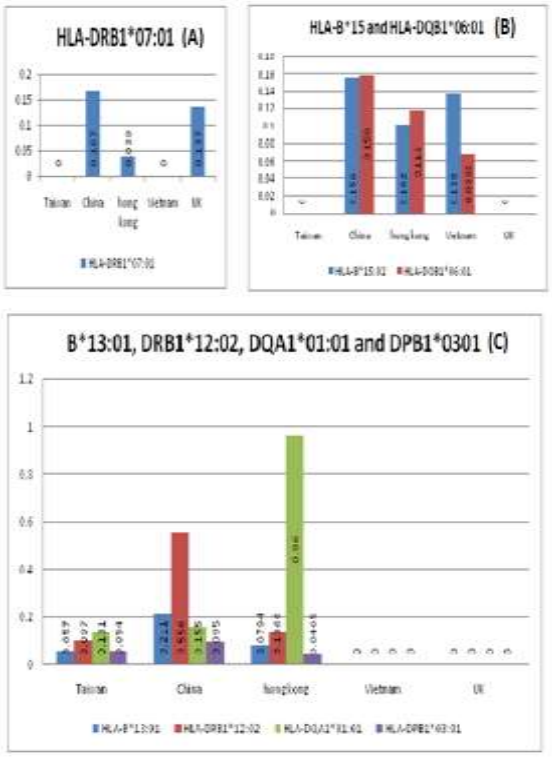

Figure 3: Common HLA Alleles in Taiwan, China, Hong Kong, Vietnam and United Kingdom A) Frequency of HLA-DRB1*07:01 B) Frequency of HLA-B* and HLA-DBQ1*06:01 C) Frequency of B*13:01, DRB1* 12:02, DQA1*01:01 and DPB1*0301

Taiwan

The most common allele in general healthy population of Taiwan is A*24: 02 in HLA-A, B*40 in HLA-B and C*03:04:01 in HLA-C while A*31:01 was associated with COVID-19 among HLA-A, its ranking was not even within first 20 frequent alleles in this population. A*30 (Frequency 0.1) was also associated with COVID-19 and its ranking was 13th (Figure 4A). Among, HLA-B, B*13 (Frequency 0.148), B*39 (0.13) and B*13:01 (0.074) (Figure 5A) were linked to the disease and their ranking was 8th, 10th and 17th according to their frequency (Figure 4B). In HLA-C, C*15:02 was found to be associated with COVID-19 patients with frequency in general population less than 0.05 and ranking wise its 14th number according to frequency (Figure 4C). Among MHC class II alleles, no associated allele was found in DQB1 while the most frequent allele in Taiwan is DQB1*03:01 (Figure 4D). In DQA1, the most frequent allele was DQA1*01:01 (frequency 0.131) (Figure 5B) and is forth highest allele (Figure 4E). In DPB1, the frequent allele is DPB1*05: 01

while the allele associated with disease is DPB1*03:01 (Frequency 0.054) (Figure 5C) and it ranks 9th according to frequency (Figure 4F). In DRB1, the most frequent allele is DRB1*04:04(frequency 0.388, ranking 1st) and the same is the most associated allele with disease, along with others such as DRB1*12 (Frequency 0.141, ranking 16), DRB1*03:01 (frequency 0.1103, ranking 23), DRB1*03:01:01 (frequency 0.082, ranking 30) (Figure 4G).

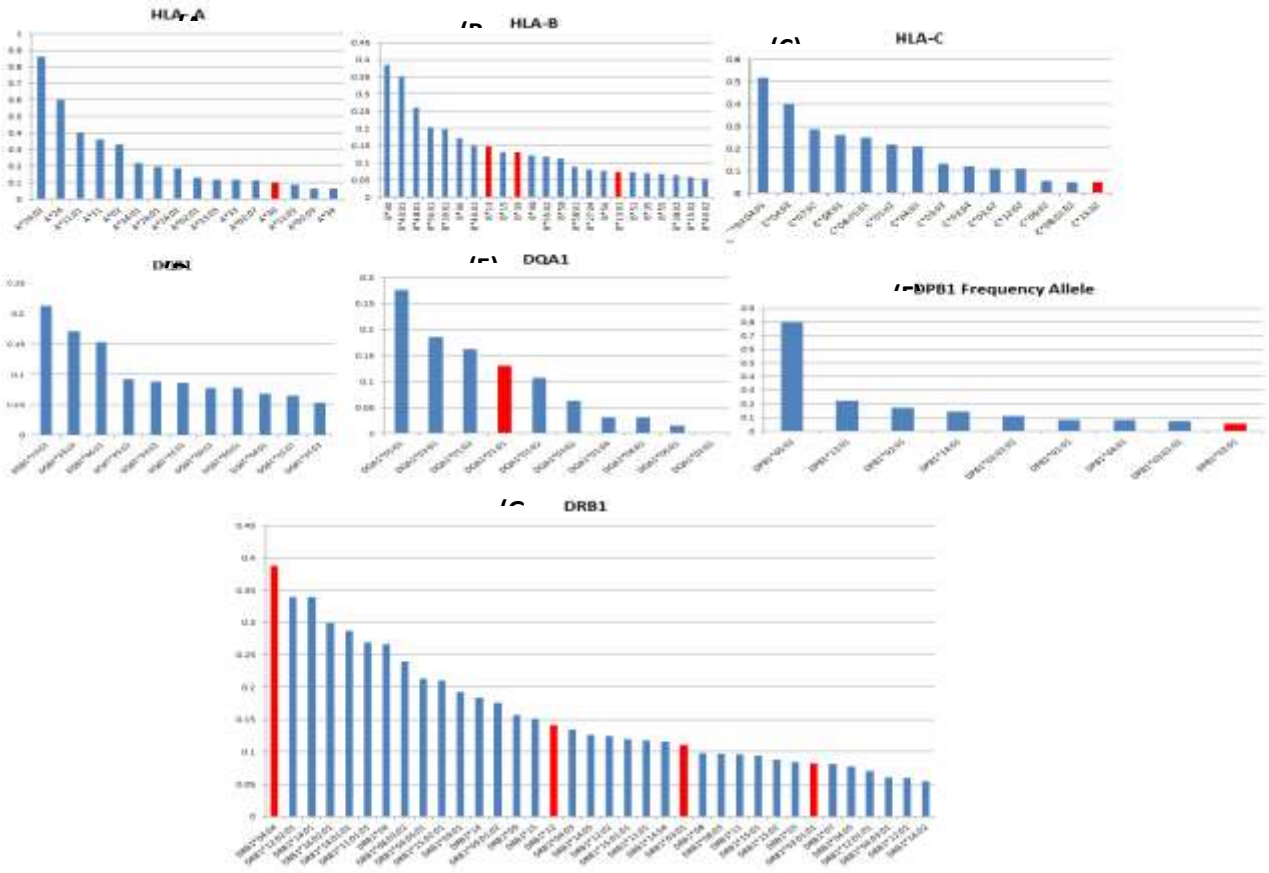

Figure 4: HLA allelic frequency in Taiwan

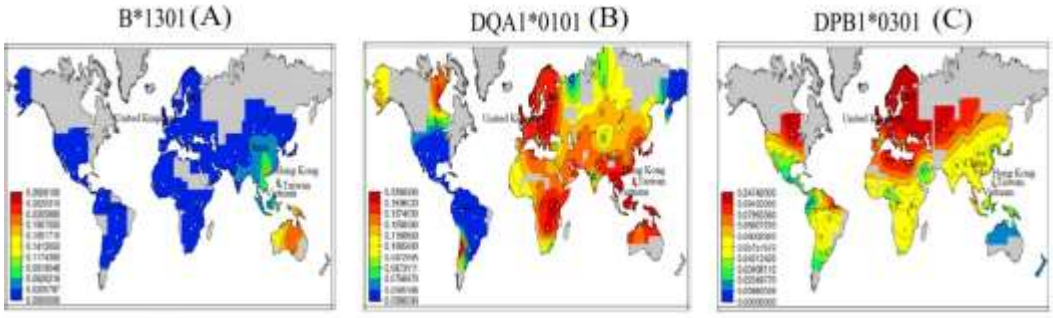

Figure 5: Maps showing Alleles associated with COVID-19 in Taiwan

China

The most common allele in general healthy population of China is A*11: 01 in HLA-A, B*13:01 in HLA-B and C*07:02 in HLA-C while A*03:01 (frequency 0.094) and A*31:01 (frequency 0.063) was associated with COVID-19 among HLA-A, its ranked at 17th & 21st frequent alleles in this population (Figure 6A). Among, HLA-B, B*13:01 (Frequency 0.211), B*15:02 (0.156), B*46:01 (0.134) B* 13:02 (0.114) B*46 (0.112) and B*54:01(0.045) were linked to the disease and their ranking was 8th, 10th and 17th according to their frequency (Figure 6B). C*08:01(0.206) was found to be associated with COVID-19 patients with frequency in general population ranking wise its 7th number according to frequency (Figure 6C). Among MHC class II alleles, In DRB1, the most frequent allele is DRB1*12:02 (frequency 0.556, ranking 2nd) and the same is the most associated allele with disease, along with others such as DRB1*07 (Frequency 0.19, ranking 6), DRB1*03:01 (frequency 0.14, ranking 15), DRB1*03:01:01 (frequency 0.125, ranking 20) (Figure 6D and 7). DQA1* 03:01 is the most frequent allele in China while DQA1*01:01 (0.155) was associated with COVID-19 (Figure 6E). In DQB1, the most frequent allele was DQB1*06:01 (frequency 0.158) and DQB1*04:02 (0.151) is ninth highest allele (Figure 6F). In DPB1, the frequent allele is DPB1*05:01:01 while the allele associated with disease is DPB1*03:01 (Frequency 0.095) and it ranks 12th according to frequency (Figure 6G).

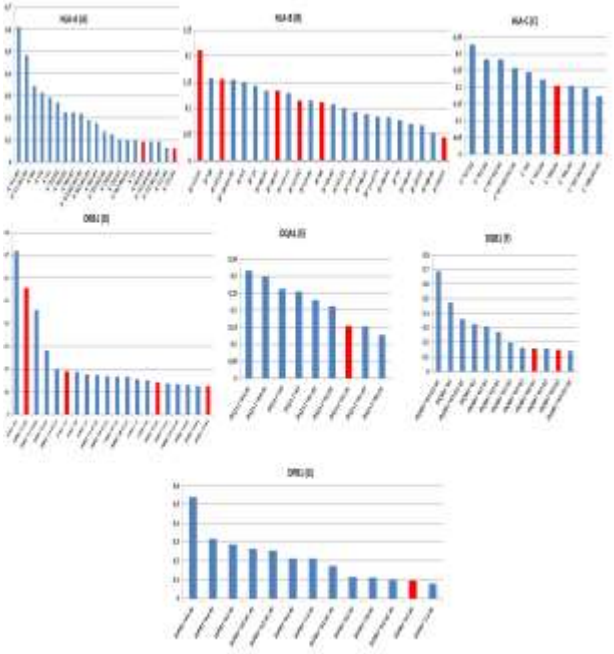

Figure 6: HLA allelic frequency in China

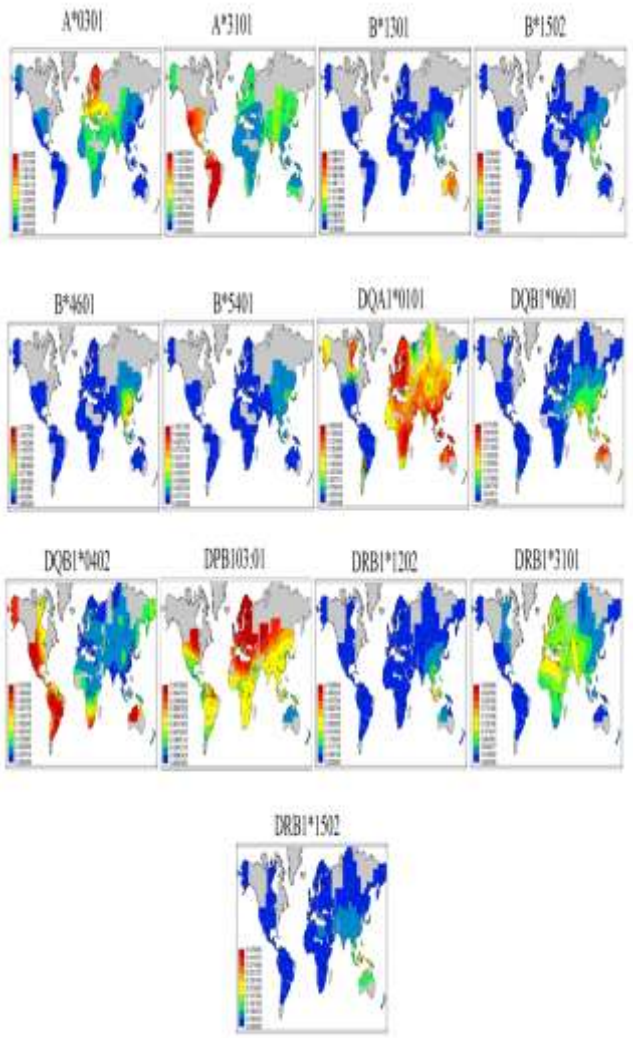

Figure 7: Maps showing Alleles associated with COVID-19 in China

Hong Kong

The most common allele in general healthy population of Hong Kong is A*11: 01 in HLA-A (Figure 8A), B*46:01 in HLA-B (Figure 8B) and C*01:02 in HLA-C (Figure 8C) while no HLA-A allele was associated with COVID-19 among this population. Among, HLA-B, B*15:02 (Frequency 0.102), B*13:01 (0.0794) were linked to the disease and their ranking was 3rd, and 5th according to their frequency. C*08:01(0.1282) & C*15:02 (0.0269) was found to be associated with COVID-19 patients with frequency in general population ranking wise its 3rd & 10th number according to frequency. Among MHC class II alleles, DQA1* 03:01 is the most frequent allele in Hong Kong while DQA1*01:01 (0.096) was associated with COVID-19 (Figure 8D). In DQB1, the most frequent allele was DQB1*06:01 (frequency 0.1189 and is 4th highest allele (Figure 8E). In DPB1, the frequent allele is DPB1*05:01 while the allele associated with disease is DPB1*03:01 (Frequency 0.0465) and it ranks 6th

according to frequency (Figure 8F). In DRB1, the most frequent allele is DRB1*12:02 (frequency 0.1369, ranking 3rd), DRB1*15:01(Frequency 0.122, ranking 4th) and DRB1*07:01 (Frequency 0.091, ranking 13) associated allele with disease (Figure 8G, 9).

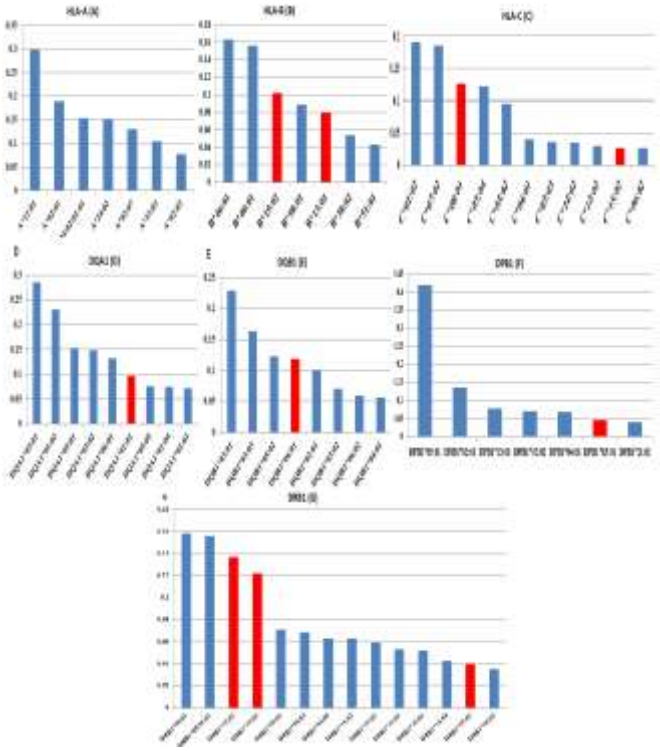

Figure 8: HLA allelic frequency in Hong Kong

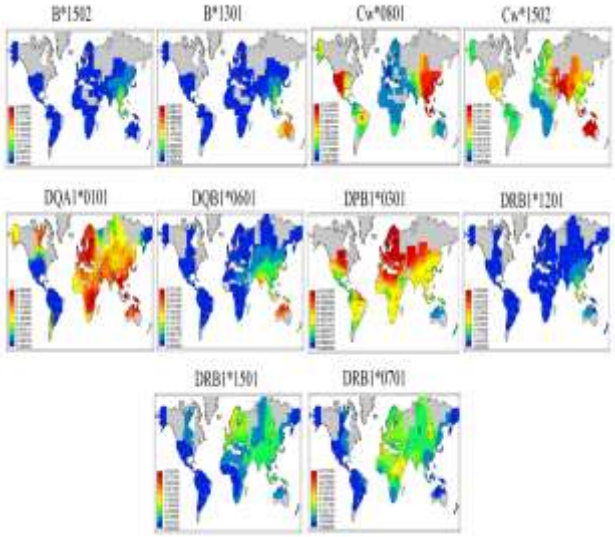

Figure 9: Maps showing Alleles associated with COVID-19 in Hong Kong

Vietnam

The most common allele in general healthy population of Vietnam is A*11 in HLA-A (Figure 10A), B*15:02 & B*46:01 in HLA-B (Figure 10B) and C*07:02:01 in HLA-C (Figure 10C) while no allele was associated with COVID-19 among HLA-A alleles in this population. Among, HLA-B, B*15:02 (Frequency 0.1383), B*46:01 (0.1194) were linked to the disease and their ranking was 1st and 2nd according to their frequency. No HLA-C allele was found to be associated with COVID-19 patients with frequency in general population. Among MHC class II alleles, in DRB1, the most frequent allele was DRB1*12:02 (frequency 0.353) and is 1ST highest allele and other associated alleles are DRB1*07: 01 (0.076), DRB1*03:01:01 (0.0743) and while the allele associated with disease is DPB1*03:01 (Frequency 0.054) and it ranks 9th according to frequency (Figure 10D). In DRB1, the most frequent allele is DRB1*12:02 (frequency 0.353, ranking 1st) and the same is the most associated allele with disease, along with others such as DRB1*07:01 (Frequency 0.076, ranking 7), DRB1*03:01:01 (frequency 0.743, ranking 8), DRB1*03:01 (frequency 0.0534, ranking 13) (Figure 10D, 11). The most frequent allele in DQB1 is DQB1*05:02:01 (0.099) (Figure 10E).

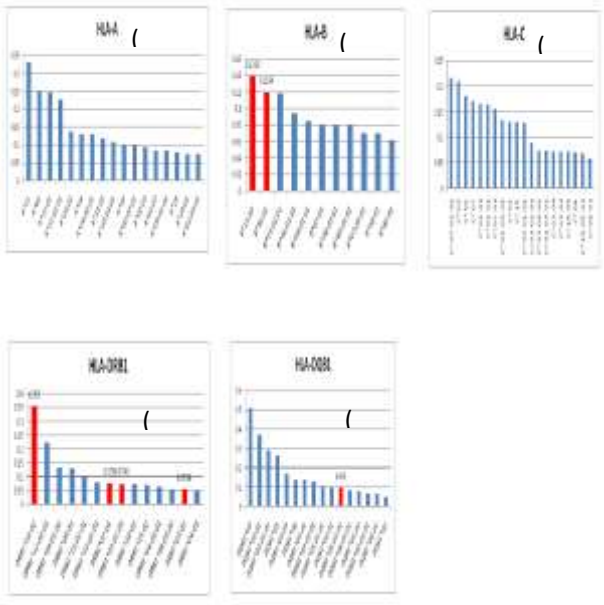

Figure 10: HLA allelic frequency in Vietnam

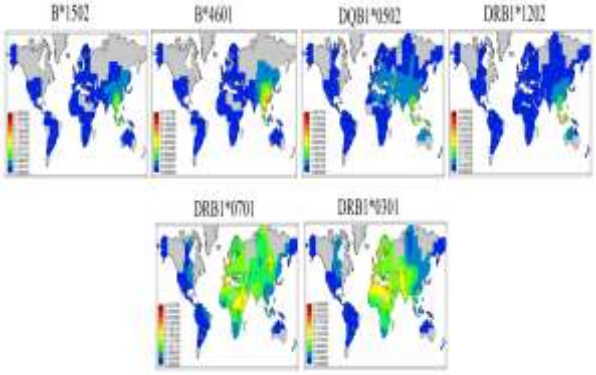

Figure 11: Maps showing Alleles associated with COVID-19 in Vietnam

United Kingdom

The most common allele in general healthy population of UK is A*02 in HLA-A (Figure 12A), B*07 in HLA-B (Figure 12B) and C*07 in HLA-C (Figure 12C). Among, HLA-A, A*03:01 Frequency (0.1366), A*29:02 (0.0352) were linked to the disease and their ranking was 2nd and 12th according to their frequency (Figure 12A). No HLA-B was found to be associated with COVID-19 patients with frequency in general population and no allele was associated with COVID-19 among HLA-C alleles in this population. Among MHC class II, in DRB1, the most frequent allele is DRB1*15:01 (frequency 0.1443, ranking 5th) and is the most associated allele with disease, along with others such as DRB1*03:01 (Frequency 0.1395, ranking 6th), DRB1*07:01 (frequency 0.1376, ranking 7th), DRB1*04:01 (frequency 0.1074, ranking 11 and DRB1*04:04 (Frequency 0.034, ranking 17) (Figure 12D, 13). In DQA1, the most frequent allele was DQA1*02:02 (frequency 0.145) and is 4th highest allele (Figure 12E). In DQB1 alleles, the most frequent allele in UK is DQB1*03 (Frequency 0.34) (Figure 12F). No allele of DQB1 is associated with disease severity. In DPA1 alleles, the most frequent allele in UK is DPA1*01 (Frequency 0.79). No allele of DPA1 is associated with disease severity (Figure 12G).

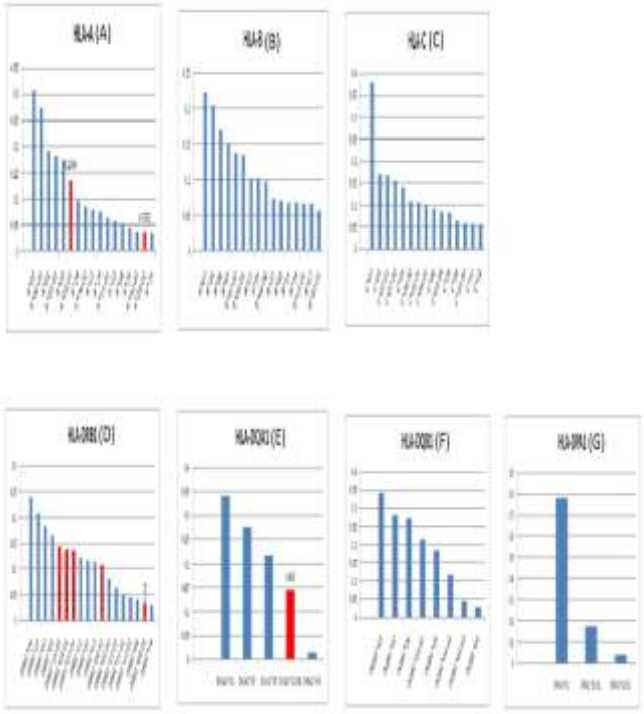

Figure 12: HLA allelic frequency in United Kingdom

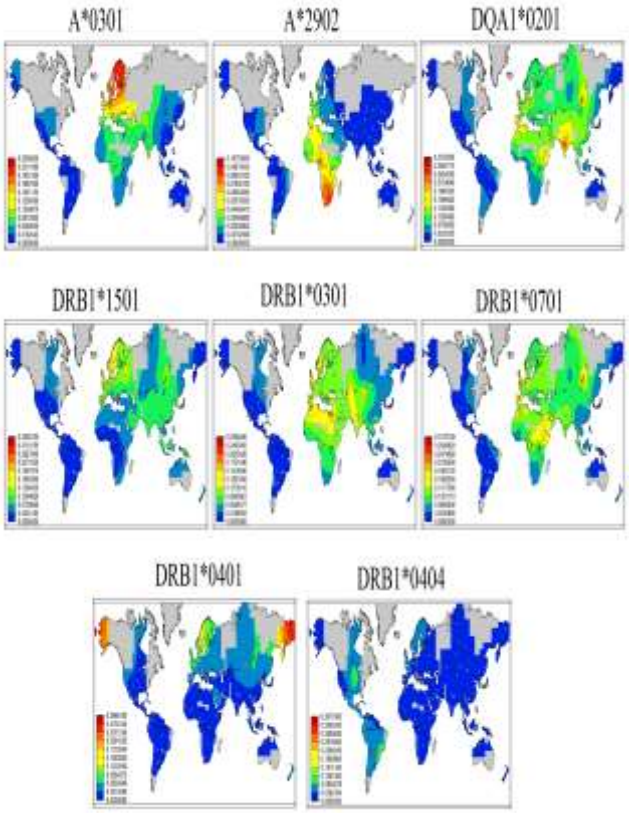

Figure 13: Maps showing Alleles associated with COVID-19 in United Kingdom

DISCUSSION

The quest of HLA association with susceptibility of COVID-19 could indeed help in development of effective vaccination against novel SARS- CoV-2. In this study we tried to utilize the information from experimental case control studies combined with the data of *in silico* analysis of correlation of HLA allele frequencies with development of COVID-19. Although environmental (non-genetic) and endogenous (genetic), both the factors are expected to influence the susceptibility to the new coronavirus SARS-CoV-2 the crucial role of HLA alleles in human populations call for thorough studies aiming at exploring on individual responses to SARS-CoV-2 infection (Stephens *et al.* 2002). COVID-19 displays significant regional/ territorial and ethnic and individual specificity proves a close correlation between the occurrence of this epidemic and the HLA system (Woo *et al.* 2009). Theoretically, the susceptible gene for coronavirus is HLA A3.1, individuals are not easily affected without this susceptible gene and will have resistance to the disease (Sanchez-Mazas, 2020; Lu *et al.* 2020). There is geographical variation, recognized in the incidence of COVID-19 with difference in immunity of different population. Variable protective HLA alleles makes the individuals of some populations resistant while presence of some alleles make some

population groups more vulnerable to COVID-19. Some HLA alleles were associated with SARS-CoV-1 during that time, but those predicted to affect SARS-CoV-2 typically exhibit remarkable diversity in other populations. For instance, HLA-A2 has several molecular subtypes that are unique to Asian, Oriental, Caucasian, and African populations (Lu *et al.* 2020).

In a recent study of Nguyen et al. 2020 the relationship between the susceptibility and /or severity of COVID-19 infection, and genetic variability among HLA-A, B, and C and were analyzed (Nguyen *et al.* 2020). In silico analysis was carried out of binding affinity between viral peptide and HLA genotypes. It was found that HLA-B*46:01 has the lowest binding affinity for COVID-19 peptides, leading to very low T-cell mediated response to the virus, consequently higher susceptibility for COVID-19 among individuals with this allele. When studied in detail HLA-B*46:01 allele found to be highly frequent in certain populations, including China, Singapore, and Taiwan (Sun and Xi, 2014). Interestingly this same HLA-B*46:01with high distribution amongst people of south east Asia is completely absent in India and Africa while certain alleles of HLA-A*02 were more frequently seen in individuals of North and central India and similarly, in European descent the HLA-C*12:03 allele seems to be the most frequent (Tomita et al. 2020). It is reflected that HLA based susceptibility to develop COVID-19 is highly variable in people from different backgrounds. Another lesser direct approach was seen in the study by Ahmed *et al.* who combined the predictive modeling with prior experimental evidence and identified SARS-CoV-1 epitopes that experimentally used T or B cell assays for confirmation (Ahmed et al. 2022). After confirmation he compared the sequence of proteins in epitopes with the corresponding sequences in SARS-CoV-2. A fully conserved corresponding HLA molecules sequence was found for the original epitopes. The study proved to be lesser effective in comparison to the bioinformatics studies.

In an attempt to develop SARS CoV-2 vaccine another bioinformatics study was conducted which investigated few HLA alleles with corresponding potential epitopes targeting non-structural protein (Basu et al. 2020). Nonetheless, four alleles implicated in this study; HLA-A*31:01, A*02:03, - DRB4*01:01 and -DRB1*07:01 and all these were used in other three studies as well (Ahmed et al. 2022; Romero-Lopez et al. 2021; Warren et al. 1996). Since Protein 4 is likely to bind MHC molecules, it was attempted that pathophysiology of COVID-19 could be explored through functional analysis of HLA-DR mediated leukocyte activation. Host genetic alterations regulate the response between host and pathogen but need further exploration. A global attempt is required to conduct thorough studies based on HLA typing and associate them with COVID-19 infection rate, severity and mortality. Genetic testing of HLA to identify the at-risk individuals may be helpful (Nguyen et al. 2020; Paik et al. 2020). Susceptible individuals who are at risk, based on HLA typing should be vaccinated against COVID-19 as a preventive measure to reduce disease spread and control strategy (Sanchez-Mazas, 2020; Debnath *et al*. 2020).

According to these research, host genetic diversity may alter the host-pathogen interaction in a way that is independent of HLA. But in our study, we also did not evaluate these options. As a result, it is important to evaluate our results carefully and continue looking into our idea. Our theory presented here might be clinically verified by including HLA typing into prospective COVID-19 clinical investigations, despite the fact that we are unable to currently access HLA genotype information for patients with COVID-19. On a worldwide scale, prospective studies are desperately needed. There is a high likelihood that these genetic pathways will interact, and the degree of that interaction will determine the risk. Depending on the frequency of risk variations and environmental exposure, this quantum of interaction will exist.

CONCLUSION

The growing recognition of genes and existing evidence of those responsible for host immune response by involving the MHC/HLA, this article helps to explore the relationship of genetic makeup of individuals with disease susceptibility, and to some extent, disease severity. Multiple HLA alleles were identified to be associated with risk of development of COVID-19. Though due to the recency of the outbreak of COVID-19, only a small number of studies are available on this topic. Still many cohort, case-control, in-silico and molecular prediction studies reveal importance of the role of various genes coding HLA, ACE2, cytokine and complement components in COVID-19. The distinct geographical pattern is an indicator of pandemic nature of COVID-19 with a great variation in its incidence and mortality. It is also uncertain that prior exposure to any other strain of coronavirus might be influencing the current geographical discrepancy. Further, the role of host genetic function would be fundamental to diagnosis, phenotypic evaluations, medication, and therapeutic response. The recent investigations of associations between HLA types in different individuals and COVID-19 infection might initiate new studies to predict the spread of coronavirus, its behavior of severity in different countries. Additionally, high risk individuals could be recognized by understanding possible variations of HLA in relation to progress of COVID-19 progress. In addition to testing for COVID -19, HLA typing could be utilized in routine to avoid potential worsening of disease and patients could even be prioritized for eventual vaccination in future.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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AUTHOR CONTRIBUTIONS

Riffat Mehboob and Fridoon Jawad Ahmad performed design, concept and analysis. Humaira Waseem performed formal analysis. Amber Hassan did the investigation. Kashifa Ehsan did original manuscript writing. Shadi Tamur designed and performed Methodology. Imran Shahid performed Visualization and proof reading. Husam Malibary performed validation of results. Maher Kurdi performed final reviewing and provided resources. All authors have read and agreed to the published version of the manuscript.

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