

HLA and COVID-19 Disease Burden

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Abstract: COVID-19 is a novel infectious disease, caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), possesses varying degree of susceptibility and lethality worldwide. The reason behind this geographical variation is likely to be multifactorial and is driven by a combination of genetic (HLA) and epigenetic factors. In this background the objective of the present discourse is to provide a complimentary overview on associations between classical HLA class I and class II molecules and susceptibility to SARS-CoV-2 and the role of HLA genetic diversity in determining the geographical distribution pattern, risk, severity, and outcomes of SARS-CoV-2 infection. Therefore, we performed a literature search reviewing pertinent articles and documents. Present review presumed that, individual HLA genotypes differentially induce the T-cell mediated antiviral response and potentially alter the course of disease and its transmission. Individuals with some HLA types are at higher risk from the disease while others remain protective. At present time when vaccination process has been started, the isolation of those individuals with high-risk HLA types could be prioritized for vaccination.

Keywords: COVID-19, HLA, Ethnic Variation, Genetic Polymorphism.

I. INTRODUCTION

COVID-19 is a novel infectious disease, caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which belongs to the family Coronaviridae [1]. From the large family of coronaviruses, SARS-CoV-2 is the seventh encountered strain that have been known to cause respiratory disease in humans [2], ranging from mild (common cold) to severe (acute respiratory disease)[3]. Nevertheless, massive global research efforts, contemporary data and perceptive, continues to generate surge of information on COVID-19 complications. Consecutive studies reported drastic systemic events taking place that contribute to the severe clinical outcomes such as; decreased hemoglobin i.e., anemia, hypoxia, altered iron metabolism, hypercoagulability, oxidative stress, cytokine storm, hyperferritinemia and multi organ failure (MOF) which are reportedly hailed as the hallmark of the COVID-19 hyper-inflammatory state [4-8]. Emerging evidence indicates that SARS-CoV-2 can also invade and attack the central nervous system (CNS) [9-10] leading to a wide repertoire of neurological symptoms and complications.

There are several genetic mediators that facilitate the SARS-CoV-2 infection in different human organs. Among them the most established one is Angiotensin-Converting Enzyme-2[11] (ACE2). The spike (S) protein of SARS-CoV-2 facilitates viral entry into the target cells which further depends on the binding of the surface unit (S1) of the S protein to a cellular receptor that facilitates viral attachment to the surface of target cells. Again, this entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2 site and allows fusion of viral and cellular membranes [12]. SARS-CoV-2 enters the human body through ACE2 receptor, present in the lung epithelial cell [11-13] and priming or activation of spike protein is relying upon transmembrane protease serine 2 (TMPRSS2) [14]. Recent data suggest that another protein termed neuropilin-1 (NRP1)[15] can potentiate infection by priming the fusion activity but only in the presence of aforementioned host factors.

Studies envisaged that, people across the globe do not all have identical immunity for protecting themselves against the coronavirus. This disease endangers disproportionately the males[16,17] and elderly especially those with pre-existing co-morbidities[18]. Furthermore, irrespective of age people with many comorbidities, including cardiovascular and pulmonary disease, diabetes appear to have higher severity and mortality by COVID-19 [17,19]. Interestingly, children seems to have lower susceptibility to the disease[20,21], possibly due to lower binding ability of the ACE2 receptor in children or generally higher levels of antiviral antibodies [22]. Nevertheless, for a pandemic situation beside age and gender, ethnicity is also another imperative factor for all kind of health and disease studies. SARS-CoV-2 infection, possesses varying degrees of susceptibility and lethality both between countries and also within countries, across different regions [17,23,24]. The highest number of case fatality rate (CFR) have been reported in Europe, followed by America, the Eastern Mediterranean, Western Pacific, South East Asia, and Africa [25]. Despite of high population densities, poor medical infrastructure, malnutrition, the countries like, South East Asia and Africa to date have witnessed comparatively lesser number of case fatality rate due to COVID-19, pointing to some innate, natural defense against SARS-CoV-2[24].

Although, the reason behind this geographical variation remains uncertain and are likely to be multifactorial and are driven by a combination of genetic [26] and epigenetic factors [27-30].

Genetic predisposition for an increased risk of SARS-CoV-2 infection is related to the expression of ACE2 [31], could shed insights into the geographical variation of this disease. ACE2 expression is associated with Angiotensin Converting Enzyme polymorphism (ACE I/D), close homologue of ACE2 [32]. Expression of this ACE2 decreases among the individuals who possess "D" allele, whereas, approximately doubled the ACE concentration among them³² which in conjugation results in a number of comorbidities including, Hypertension, Diabetes, Cardiovascular disease [33,34] thus the severity of COVID-19 infection [18]. The ACE I/D polymorphism discerned important geographical variation [35]. Although the outbreak of SARS-CoV-2 emerged in Asian countries but after that European countries and USA experienced much higher incidence of morbidity and mortality rate [25]. Studies [36-38] reported that, frequency of the D-allele is higher in Europe, Southern Europe and USA, compared to Asia and particularly India, hoist intuitive phenomenon behind the higher frequency of morbidity and mortality among the Europeans than in the Asians.

Besides this, genetic variations in immune function-related genes such as human leukocyte antigen (HLA) are emerging as a critical determinant of COVID-19 infection progression [3,25] as well as geographical variation [39]. HLAs are proteins encoded by a diverse set of human genes in the major histocompatibility complex (MHC) [3,25] and are a critical component of the viral antigen presentation pathway [3]. HLA is divided into three classes, I, II & III [40,41]. HLA class I proteins are responsible for coding the molecules like, HLA-A, -B, -C, -E, -F and -G present in almost all somatic cells [40-42]. The class II proteins code the molecules like, HLA-DR, -DQ, -DM and -DP, expressed in a subgroup of antigen-presenting immune cells, including B cells, activated T cells, macrophages, dendritic cells and thymic epithelial cells [40-41] and finally the class III molecules encode complement proteins that interact with antibody-antigen complexes and induces cell lysis [42]. The classical HLA loci are the class I and class II molecules that are identified for their role in presentation of antigen to CD8+ and CD4+ T cells respectively and also for recognition of self-versus non-self [25-39]. They are encoded by a 4-Mb region of human chromosome 6p21 that is recognized as the most variable region in the human genome [43]. HLA molecules are positioned on the surface of cells, and serves as receptors for viral peptides, as they present the peptides to the virus-specific cytotoxic T lymphocytes [25]. There are several hypotheses about the mechanism of HLA and disease association, possibly which varies for different diseases. Among them one of the hypotheses is; greater or less affinity of HLA for the disease-causing peptide [44] i.e., when a virus infects an organism, the invader's proteins are first cut into small fragments called peptides. Then the HLA molecules bind with these fragments and expose them to the surface of the cells, CD8+ T cells recognize the conformational structure of the peptide binding groove of the MHC class I molecules, bound to an antigenic peptide, recognizes the self or non-self and thereby triggering a cascade of immunity reactions designed to eliminate the virus. Variation in the conformational structure of the peptide binding groove and its binding to varied peptides are determined by variations within HLA (Class I, II) genes [45]. This HLA genes exhibit extreme diversity and have several thousand reported polymorphisms [41,46] with numerous alleles with various possible combinations. This polymorphism contributes to the genetic diversity of the species and to the differences in susceptibility to diseases among genetically distinct groups [47].

Since, the discovery [48], HLA loci have stood out as the leading candidates for infectious disease susceptibility. A few studies also carried out on HLA association with SARS-CoV-1 [49-52]. HLA alleles like, HLA-B*46:0 [49], HLA-B*07:03 [50], HLA-C*08:01 [51], and HLA-DRB1*1202 [52] were considered as a risk allele for SARS-CoV-1 while several other alleles like; HLA-DRB1*03:01 [50], HLA-C*15:02, and HLA-DRB1*03:01 [53] provided protection against this disease. In addition to this, multiple functional studies [54,55] identified HLA-A*0201 T cell epitopes from SARS-CoV nuclear capsid and spike proteins for severe outcome. Besides this, associations between HLA genotypes and increase or decrease risk of disease severity extend broadly to several other unrelated viruses, for example, Hepatitis B [56-58], Hepatitis C [56,59-61], human immunodeficiency virus (HIV) [62-64], Tuberculosis [65-67], Schistosomiasis [68], Dengue [69]. Therefore, it can be said that, variability in HLA genes are crucial in MHC-peptide interactions and in differential susceptibilities to viral infection and also in transplant immunity [70].

II. OBJECTIVE

In this background the objective of the present discourse is to provide a complimentary overview on associations between classical HLA class I and class II molecules and susceptibility to SARS-CoV-2 and the role of HLA genetic diversity in determining the geographical distribution pattern, risk, severity, and outcomes of SARS-CoV-2 infection.

III. MATERIAL AND METHODS

Therefore, we performed a literature search reviewing pertinent articles and documents. PubMed, Google Scholar and ResearchGate were investigated using the following headings and keywords, linked to the word COVID-19 or SARS-CoV-2: origin, spike protein, ACE2 receptor, ACE I/D polymorphism, Immunity, HLA, MHC, genotypes, locus, genes,

alleles, epitope, pathogenesis, immunology, cytokines, mortality, morbidity, geographical variation, humoral response, T cells, B cells.

IV. ANALYSIS OF LITERATURES

There is a growing recognition that HLA, being the critical regulator of immune response to viral infections, may play a crucial role in differential susceptibility to SARS-CoV-2 infection [71] and this is strengthened by the study on 28 patients suffering from COVID-19 induced severe respiratory failure, where the patients represented lower expression of HLA-DR accompanied by profound reduction of CD4, CD19 lymphocytes and natural killer (NK) cells [72]. A large number of different HLA alleles were studied by many [3,73-76] to find out the binding affinity of the alleles with SARS-CoV-2 peptide and its presenting capacity to T cells.

An *in silico* analysis [73] suggested higher binding tendency of SARS-CoV peptide to HLA-A: 02:01. Efforts are also being made by another study [76] to predict the MHC class I epitope landscape using SARS-CoV-2 viral proteomes and found some epitopes of SARS-CoV-2 were associated with five distinct HLA alleles, such as HLA-A*02:01, HLA-B*40:01, HLA-DRA*01:01, HLA-DRB1*07:01, and HLA-DRB1*04:01. Another study [74] confirmed the association of all these HLA class I peptides with SARS-CoV-2. Furthermore, bioinformatics prediction and molecular modeling study [75] identified HLA-A*02:03 and A*31:01 as highly effective antigen presenters for SARS-CoV-2, implying that these would provide protection, while, HLA-A*03:02 appeared as a risk allele. Subsequent to this, another *in silico* analysis [3] have been done on binding affinity of MHC class I molecules with viral peptide across 145 HLA-A, -B, and -C genotypes for all the peptides of SARS-CoV-2 and observed that, the HLAB*46:01 allele could increase susceptibility to COVID-19, as this allele had fewest predicted binding peptides for SARS-CoV-2 while in contrast HLA-B*15:03 could provide T cell-based protective immunity as this allele displayed highest capacity to present highly conserved SARS-CoV-2 peptides. This study also reported that at haplotype level, HLA-A*02:02, HLA-B*15:03, and HLA-C*12:03 exhibited highest and HLA-A*25:01, HLA-B*46:01, and HLA-C*01:02 displayed lowest predicted repertoire of epitopes from SARS-CoV-2 (Fig: 1). Another study found that B*15:27 alleles may be associated with the occurrence of COVID-19 [77].

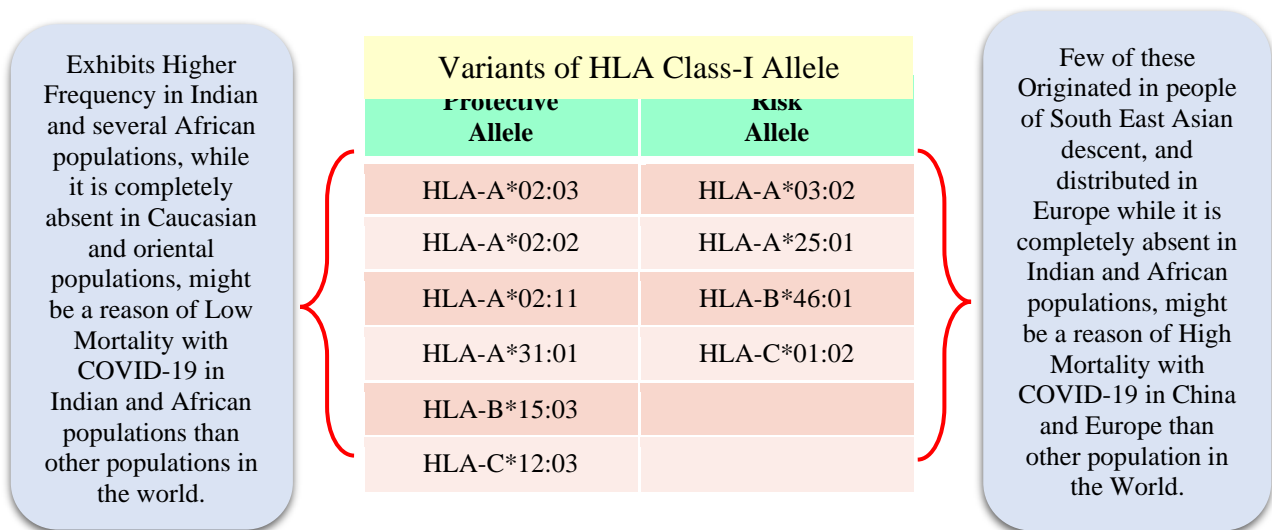


Fig: 1. Distribution of HLA Alleles in different ethnic population and their association with COVID-19 severity

The frequency of these HLA alleles varies from one population to another due to past migrations and their adaptation to different environments [78,79]. This variation in HLA allele distribution along with distinct pattern of geographical variation in the incidence of COVID-19 indicated that population-specific HLA alleles act as an intrinsic determinant of protective immunity against SARS-CoV-2 and make some individuals and/or population resistant or vulnerable to this disease [25]. For example, HLA-A*02 allele and its several molecular subtypes are mainly found in Caucasian, African, Oriental, and Asian populations [80]. A recent study in North and central Indian populations on certain alleles of HLA-A*02 such as, A*02:01, *02:03, *02:05, *02:06, *02:07, and *02:11 were shown to have high frequencies. Among these A*02:11 exhibited highest occurrence at the repertoire level [81] seems to be common in Indian populations but it is completely absent in Caucasian and Oriental populations. Although the frequency and diversity of certain alleles of HLA-A*02 reported to be high in African populations [82]. These HLA-A*02 subtypes are predicted to be protective against SARS-CoV-2 infection [74-76] which exhibits higher frequency in Indian and several African populations may be a

possible reason of comparatively less severity due to COVID-19 in Indian and African populations than European and other world populations, although in the USA, people of African descent have been hardest hit [83]. Furthermore, HLA-B*46:01 allele which is known to increase the susceptibility to COVID-19 [3], interesting to note that HLA-B*46:01 originated in people of South East Asia, and has high distribution in South East Asia [84], while it is completely absent in Indian and African populations and rarely present in European populations. Similarly, the protective allele, HLA-B*15:03 [3] is completely absent in East Asian gene pool while it is the most frequent allele in populations of African descent. Again, the susceptibility allele, HLA-C*12:03 seems to be the most frequent allele in the European descent. This explains partially why the susceptibility of COVID-19 varies in people from different backgrounds.

V. CONCLUSION

From the present narrative it can be concluded that, individual HLA genotypes may differentially induce the T-cell mediated antiviral response and could potentially alter the course of disease and its transmission. Individual genetic variation may help to explain different immune responses to a virus across a population. In particular, understanding how variation in HLA may affect the course of COVID-19 could help identify individuals at higher risk from the disease. At present time when vaccination process has been started, the isolation of individuals with high-risk HLA types could be prioritized for vaccination.

VI. LIMITATION

Despite of having protective HLA (HLA-A*02) allele subtypes, America's Indigenous populations face a devastating effect of COVID-19 while on the other hand European population which is devoid of the risk allele (HLA-B*46:01) suffer from high rate of CFR due to COVID-19, indicates HLA is far from being the only element that can be used to predict effective or ineffective resistance to a virus, require more studies in this regard.

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REFERENCES

- [1]. Gorbalenya AE, Baker S, Baric R, Groot RJ, Drosten C, et al. The species Severe Acute Respiratory Syndrome-related Coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. *Nat Microbiol* 2020; 5(4): 536-544.
- [2]. Zhu N, Zhang D, Wang W, Li X, Yang B, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020; 382(8):727-733.
- [3]. 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. *Journal of Virology* 2020; 94(3): 1-12.
- [4]. Taneri PE, Gómez-Ochoa SA, Llanaj E, Raguindin PF, et al. Anemia and iron metabolism in COVID-19: a systematic review and meta-analysis. *Eur J Epidemiol* 2020; 35(8):763-773.
- [5]. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; 395: 1033-1034.
- [6]. Phua J, Weng L, Ling L, Egi M, Lim C, Divatia JV, et al. Intensive care management of coronavirus disease 2019 (COVID-19): Challenges and recommendations. *Lancet Respir Med* 2020; 8(5): 506-517.
- [7]. Zaim S, Chong JH, Sankaranarayanan V, Harky A. COVID-19 and multiorgan response. *Curr Probl Cardiol* 2020; 45(8): 1-22.
- [8]. Ghosh K, Chatterjee D, Ghosh Roy A, Bandyopadhyay Arup R. Socio-economic Status, Iron Deficiency anemia and COVID-19: An Appraisal. *European Journal of Clinical and Experimental Medicine* 2021; 19(1): 52-58.
- [9]. De Felice FG, Tovar-Moll F, Moll J, Munoz DP and Ferreira ST. Severe acute respiratory Syndrome coronavirus 2 (SARS-CoV-2) and the central nervous System. *Trends Neurosci* 2020;43(6): 355-357.
- [10]. Mao XY and Jin W. The coVid-19 Pandemic: consideration for brain infection. *Neuroscience* 2020; 437: 130-131.
- [11]. Wan Y, Shang J, Graham R, Baric RS and Li F. Receptor recognition by novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS. *J Virology* 2020; 94(7):
- [12]. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* 2020; 181(2): 271-280.
- [13]. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, Li F. Cell entry mechanisms of SARS-CoV-2. *Proc Natl Acad Sci USA* 2020; 117(21): 11727-11734.
- [14]. Iwata-Yoshikawa N, Okamura T, Shimizu Y, Hasegawa H, Takeda M and Nagata N. TMPRSS2 contributes to virus spread and immunopathology in the airways of murine models after coronavirus infection. *Journal of Virology* 2019; 93(6): e01815-18.
- [15]. Cantuti-Castelvetri L, Ravi Ojha R, Pedro LD, Djannatian M, et al. Neuropilin-1 facilitates SARS-CoV-2 cell entry and infectivity. *Science* 2020; 370(6518): 856-860.
- [16]. Jin JM, Bai P, He W, Wu F, Liu X, Han D, Liu S, Yang J. Gender Differences in Patients with COVID-19: Focus on Severity and Mortality. *Frontiers in Public Health* 2020;8(152):1-6.
- [17]. Bandyopadhyay AR, Chatterjee D, Ghosh K, Sarkar P. COVID 19: An Epidemiological and Host Genetics Appraisal. *Asian Journal of Medical Sciences* 2020; 11(3):71-76.
- [18]. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, Ji R, Wang H, Wang Y, Zhou Y. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis. *Int J Infect Dis* 2020; 94: 91-95.
- [19]. Guan W-J, Liang W-H, Zhao Y, Liang H-R, Chen Z-S, Li Y-M, et al. Comorbidity and its impact on 1,590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020; 55(5): 2000547.

- [20]. Cao Q, Chen Y-C, Chen C-L, Chiu C-H. SARS-CoV-2 infection in children: transmission dynamics and clinical characteristics. *J Formos Med Assoc* 2020; 119(3): 670–673.
- [21]. Lu X, Zhang L, Du H, Zhang J, Li YY, Qu J, Zhang W, et al. SARS-CoV-2 infection in children. *N Engl J Med* 2020; 382(17):1663-1665.
- [22]. Dong Y, Mo X, Hu Y, Qi X, Jiang F, Jiang Z, Tong S. Epidemiological characteristics of 2143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics* 2020; 147(4): e20200702.
- [23]. Dhillion P, Kundu S, Shekhar C, Ram U, Dwivedi LK, Yadav S, Unisa S. Case-Fatality Ratio and Recovery Rate of COVID-19: Scenario of Most Affected Countries and Indian States. *International Institute for Population Sciences Mumbai* 2020; 1-19.
- [24]. Ghosh K, Roy AG, Chatterjee D, Bandyopadhyay AR. 2021. A multidisciplinary approach to COVID-19 with special reference to North-east India: Genetic factors and beyond. *Human Diversity in North-east India, Bio-anthropological Approaches*. Edited by Sarthak Sengupta and Dali Dutta. Chapter 20, pp-249.
- [25]. Debnath M, Banerjee M, Berk M. Genetic gateways to COVID-19 infection: Implications for risk, severity, and outcomes. *The FASEB Journal* 2020; 34(7):8787–8795.
- [26]. Anastassopoulou C, Gkizarioti Z, Patrinos GP, Tsakris A. Human genetic factors associated with susceptibility to SARS-CoV-2 infection and COVID-19 disease severity. *Human Genomics* 2020; 14(40): 2-8.
- [27]. Esteve A, Permanyer I, Boertien D, Vaupel JW. National age and co-residence patterns shape covid-19 vulnerability. *Proc Natl Acad Sci U S A* 2020; 117(28):16118-16120.
- [28]. Singh R, Adhikari R. Age-structured impact of social distancing on the COVID-19 epidemic in India. Preprint 2020.
- [29]. Rocklov J, Sjodin H. High population densities catalyze the spread of COVID-19. *J Travel Med* 2020; 27(3):taaa038.
- [30]. Dudel C, Riffe T, Acosta E, Raalte AV, Strozza C, Myrskylä M. Monitoring trends and differences in COVID-19 case fatality rates using decomposition methods: Contributions of age structure and age-specific fatality. *PLoS ONE* 2020; 15(9): 1-11.
- [31]. Zhao Y, Zhao Z, Wang Y, Zhou Y, et al. Single-Cell RNA Expression Profiling of ACE2, the Receptor of SARS-CoV-2. *Am J Respir Crit Care Med* 2020; 202(5): 756–759.
- [32]. Pinheiro DS, Santos RS, Veiga Jardim PCB, Silva EG, Reis AA, Pedrino GR, Ulhoa CJ. The combination of ACE I/D and ACE2 G8790A polymorphisms reveals susceptibility to hypertension: A genetic association study in Brazilian patients. *PLoS One* 2019;14(8): 1-15.
- [33]. Gard PR. Implications of the angiotensin converting enzyme gene insertion/deletion polymorphism in health and disease: a snapshot review. *Int J Mol Epidemiol Genet* 2010;1(2): 145-157.
- [34]. Ghosh K, Sarkar P, Chatterjee D, Bandyopadhyay AR. Association of fat patterning, hypertension and ACE (I/D) gene polymorphism: a study on two Tibeto-Burman linguistic group of Tripura, North East India. *MOJ Anat & Physiol* 2018; 5(6):368–371.
- [35]. Saab YB, Gard P, Overall A. The geographic distribution of the ACEII genotype: anovelfindingGenet Res2007; 89(4): 259-267.
- [36]. Delanghe JR, Speeckaert MM and De Buyzere ML. The host's angiotensin-converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections. *Clin Chim Acta* 2020; 505: 192-193.
- [37]. Kenyon C. ACE-I I/D polymorphism associated with COVID-19 incidence and mortality: an ecological study. Preprints 2020.
- [38]. El Ezzi AA, Clawson JM, El-Saidi MA, Zaidan WR, Kovash A, Orellana J, Thornock A, Kudduset RH. Association of Angiotensin I Converting Enzyme insertion/287 bp Deletion polymorphisms and proliferative Prostatic diseases among Lebanese Men. *Prostate Cancer* 2020; 2020(9): 1-6.
- [39]. Blackwell JM, Jamieson SE, Burgner D. HLA and infectious diseases. *Clin Microbiol Rev* 2009; 22(2):370-385.
- [40]. Fernandes A, Maciel L, Foss M, Donadi EA. Como entender a associação entre o sistema HLA e as doenças auto-imunes endócrinas. *Arq Bras Endocrinol Metab* 2003; 47(5):601- 611.
- [41]. Klein J, Sato A. The HLA System - First of two parts. *N Engl J Med* 2000; 343(11):702-9.
- [42]. Choo SY. The HLA System: Genetics, Immunology, Clinical Testing, and Clinical Implications. *Yonsei Med J* 2007; 48(1): 11–23.
- [43]. Horton R, Gibson R, Coghill P, Miretti M, et al. Variation analysis and gene annotation of eight MHC haplotypes: the MHC Haplotype Project. *Immunogenetics* 2008;60(1):1–18.
- [44]. Alves C, Vieira N, Meyer I, Alves CO, et al. Human histocompatibility antigens and Dermatology: from research to clinical practice. *An Bras Dermatol* 2006;81(1):65-73.
- [45]. Tavasolian F, Rashidi M, Hatam GR, Jeddi M, Hosseini AZ, Mosawi SH, Abdollahi E and Inman RD. HLA, Immune Response, and Susceptibility to COVID-19. *Front. Immunol.* 2021; 11:601886.
- [46]. Markov PV, Pybos OG. Evolution and Diversity of the Human Leukocyte Antigen(HLA). *Evol Med Public Health.* 2015; 2015(1): 1.
- [47]. Van Rood JJ. The impact of the HLA-system in clinical medicine. *Shweiz Med Wschr* 1993;123(3):85-92.
- [48]. Thorsby E. The human major histocompatibility system. *Transplant. Rev* 1974; 18:51–129.
- [49]. Lin M, Tseng HK, Trejaut JA, et al. Association of HLA class I with severe acute respiratory syndrome coronavirus infection. *BMC Med Genet.* 2003;4(9): 1-7.
- [50]. Ng MH, Lau KM, Li L, et al. 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):515-518.
- [51]. Chen YM, Liang SY, Shih YP, et al. 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):359-365.
- [52]. Keicho N, Itoyama S, Kashiwase K, et al. Association of human leukocyte antigen class II alleles with severe acute respiratory syndrome in the Vietnamese population. *Hum Immunol.* 2009;70(7):527-531.
- [53]. Wang SF, Chen KH, Chen M, et al. 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):421-426.
- [54]. Wang B, Chen H, Jiang X, et al. Identification of an HLA-A*0201- restricted CD8+ T-cell epitope SSp-1 of SARS-CoV spike protein. *Blood* 2004;104(1):200-206.
- [55]. Tsao YP, Lin JY, Jan JT, et al. HLA-A*0201 T-cell epitopes in severe acute respiratory syndrome (SARS) coronavirus nucleocapsid and spike proteins. *Biochem Biophys Res Comm.* 2006;344(1):63-71.
- [56]. Singh R, Kaul R, Kaul A, Khan K. A comparative review of HLA associations with hepatitis B and C viral infections across global populations. *World J. Gastroenterol.* 2007; 13(12):1770–1787.
- [57]. Thio CL, Thomas DL, Karacki P, et al. Comprehensive analysis of class I and class II HLA antigens and chronic hepatitis B virus infection. *J Virol* 2003;77(22):12083-12087.
- [58]. Jiang YG, Wang YM, Liu TH, Liu J. Association between HLA class II gene and susceptibility or resistance to chronic hepatitis B. *World J Gastroenterol* 2003;9(10):2221-5.
- [59]. Thio CL, Thomas DL, Goedert JJ, et al. Racial differences in HLA class II associations with hepatitis C virus outcomes. *J Infect Dis* 2001;184(1):16-21.
- [60]. Thio C.L., Gao X., Goedert J.J., et al. HLA-Cw*04 and hepatitis C virus persistence. *J Virol* 2002;76(10):4792-4797.
- [61]. McKiernan SM, Hagan R, Curry M, et al., Distinct MHC class I and II alleles are associated with hepatitis C viral clearance, originating from a single source. *Hepatology* 2004;40(1):108-114.

- [62]. McMichael, A., and P. Klenerman. HIV/AIDS. HLA leaves its footprints on HIV. *Science* 2002; 296(5572):1410–1411.
- [63]. Gao X, Nelson GW, Karacki P, et al. Effect of a single amino acid change in MHC class I molecules on the rate of progression to AIDS. *N Engl J Med.* 2001;344(22):1668-1675.
- [64]. Paranjape RS. Immunopathogenesis of HIV infection. *Indian J Med Res* 2005;121(4):240-55.
- [65]. Rajalingam R, Mehra NK, Jain RC, et al. Polymerase chain reaction-based sequence-specific oligonucleotide hybridization analysis of HLA class II antigens in pulmonary tuberculosis: relevance to chemotherapy and disease severity. *J Infect Dis* 1996;173(3):669-676.
- [66]. Amirzargar AA, Yalda A, Hajabolbaghi M, et al. The association of HLA-DRB, DQA1, DQB1 alleles and haplotype frequency in Iranian patients with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2004;8(8):1017-21.
- [67]. Alves C, Souza T, Meyer I, Maria Betânia P, et al. Immunogenetics and Infectious Diseases: Special Reference to the Mayor Histocompatibility Complex. *The Brazilian Journal of Infectious Diseases* 2006; 10(2):122-131.
- [68]. Salam EA, Ishaac S, and Mahmoud AA. Histocompatibility-linked susceptibility for hepatosplenomegaly in human schistosomiasis mansoni. *J Immunol* 1979;123(4):1829-31.
- [69]. Loke H, Bethell DB, Phueng CX, et al. Strong HLA class I—restricted T cell responses in dengue hemorrhagic fever: a double-edged sword? *J Infect Dis* 2001;184(11):1369-73.
- [70]. Barouch DH, Kunstman J, Kuroda MJ, Schmitz JE, et al. Eventual AIDS vaccine failure in a rhesus monkey by viral escape from cytotoxic T lymphocytes. *Nature* 2002; 415(6869):335–339.
- [71]. Sanchez-Mazas A. HLA studies in the context of coronavirus outbreaks. *Swiss Med Wkly.* 2020;150:w20248.
- [72]. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe* 2020; 27(6): 992-1000.
- [73]. Hyun-Jung Lee C, Koohy H. In silico identification of vaccine targets for 2019-nCoV. *F1000Research* 2020;9(145):1-15.
- [74]. Campbell KM, Steiner G, Wells DK, Ribas A, and Kalbasi A. Prediction of SARS-CoV-2 epitopes across 9360 HLA class I alleles. *BioRxiv.* 2020.
- [75]. Romero-Lopez JP, Carnalla-Cortes M, Pacheco-Olvera DL, et al. Prediction of SARS-CoV spike protein epitopes reveals HLA-associated susceptibility. *Res Square.* 2020.
- [76]. Ahmed SF, Quadeer AA, and McKay MR. Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARSCoV-2) based on SARS-CoV immunological studies. *Viruses* 2020;12(3): 254.
- [77]. Wang W, Zhang W, Zhang J, He J, and Zhu F. Distribution of HLA allele frequencies in 82 Chinese individuals with coronavirus disease-2019 (COVID-19). *HLA.* 2020;1–3.
- [78]. Buhler S and Sanchez-Mazas A. HLA DNA sequence variation among human populations: molecular signatures of demographic and selective events. *PLoS One* 2011;6(2):e14643.
- [79]. Mazes S and Meyer A. The relevance of HLA sequencing in population genetics studies. *Journal of Immunology Research* 2014; 2014(971818): 1-12.
- [80]. Middleton D, Williams F, Meenagh A, et al. Analysis of the distribution of HLA-A alleles in populations from five continents. *Hum Immunol* 2000;61(10):1048-1052.
- [81]. Saxena A, Sharma G, Tyagi S, et al. 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.
- [82]. Cao K, Moormann AM, Lyke KE, et al. Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci. *Tissue Antigens.* 2004;63(4):293-325.
- [83]. Yancy CW. COVID-19 and African Americans. *JAMA* 2020; 323(19):1891–1892.
- [84]. González-Galarza F, Takeshita L, Santos E, et al. Allele frequency net 2015 update: new features for HLA epitopes, KIR and disease and HLA adverse drug reaction associations. *Nucleic Acids Res.* 2015;43:784-788.