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Review Article

Does human leukocyte antigen gene polymorphism affect management of COVID-19 Patients? A review article

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Abstract

New corona virus disease (COVID-19) is a recent worldwide pandemic occurred as a result of SARS-CoV-2 virus, where, it spreads mainly through large respiratory droplets, and probability of other routes of transmission do exist, due to the suspicion of the viral abundance in feces and urine of affected individuals [1]. The transfer and transmission of COVID-19 is high and occurs via respiratory secretions, where, the virus invades the body through the inner wall cells of upper respiratory tract causing severe injury of the lungs, affecting its performance, and consequently respiration efficiency [2].

Transmission between individuals occurs mainly through direct contact or droplets spread by sneezing or coughing from carrier individual which is accompanied by binding of SARS-COV spikes to the ACE2 cellular receptor expressed by lung epithelial cells which is the first step of the viral infection followed by fusion with the cell membrane. Concerning the clinical findings of COVID-19 infection, it was found that there is an increased levels of plasma pro-inflammatory cytokines like IL1-β, IL1RA, IL7, IL8, IL9, IL10, TNFα, leucopenia, elevated C-reactive protein, elevated D-dimer, and high ESR [3].

However, most of the infected patients showed a mild clinical presentation of the disease, while others have developed severe signs and symptoms characterized by respiratory compromise [4]. It is well-known that the genome is the human DNA, his /her genes and their expressions which in turn give the different specific characteristic of the human being. Moreover, the thousands of genetic variations among people are reported for each allele which is called Snips (SNPs).

In fact, diploid people with two different alleles types known as (Heterozygous) are more likely to develop polymorphism, than those with the same allele type (Homozygous), especially in those environments rich with pathogens. It is assumed that different Human Leukocyte Antigen (HLA) molecules are supporting potential to present peptides derived from pathogens are due to T-lymphocytes, and so triggering an immune reaction.

Introduction

Human Leukocyte Antigen genes are having high variations among different populations, where, the majority of human beings HLA locus are showing about 85% and 95% heterozygous characteristic at each locus [5]. Hereby, we are going to present shortly and in summary the role and effect of variants alleles of HLA, on severity and incidence of infection with COVID-19, and its management as well.

It was remarked that SARS-CoV patients who are suffering from hepatic inflammation of viral origin are more vulnerable to progression leading to liver damage and serious acute hepatic inflammation, and thus it was explained on the basis that progression is probably due to an increase in hepatitis virus replication in parallel to SARS-COV-2.

On this basis, some of the HLA genes class II haplotypes, like DRB1*1302, HLA-DR13, DQA1*0501, and DQB1*0301 have been also related to hepatitis B virus endurance [6]. Consequently, a great benefit will result upon studying alleles sharing the risk that might exist between hepatitis virus and corona virus. A recent study in Wuhan- China which suggested the possibility of involvement of the two classes (I) and (II) alleles of HLA at

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the initial stage of the COVID-19 epidemic, where, the obtained results indicated that HLA-II estimations from the specimens of Broncho alveolar lavage showed to be the highest for HLA class II genes DP-A1, and B1, DQ-A1, and B1, DR-A, B1, B3, B4 and B5 [7].

In order to get a conclusion, from reviewers point of view, concerning genomic and/or genetics studies, gathering of information from several studies performed on different populations, races and ethnics and consequently with different genomes leading to human beings' variations as a result of different genes expressions, populations' behaviors and their clinical presentation when infected with COVID-19 and other diseases and therefore patients' response to management protocols used.

Clinical studies and discussion

Herein, some studies will be presented including different population with different genomes as well to investigate the relationship between HLA polymorphisms and different diseases which might be correlated to the severity and/or incidence of COVID-19, and thus, imposing specific population more vulnerable to infection than other.

A cohort study performed in United Kingdom on Caucasian patients, where, HLA-II polymorphism analysis showed a significant correlation between it and the development of spontaneous bronchiectasis of unknown origin, suggesting the involvement of patients immunity system specially the T cells in respiratory tissue damage [8].

Concerning COVID-19 disease, the antigen presentation is almost done by major histocompatibility complex (MHC-I) followed by MHC-II. It was reported that coronavirus infects macrophages due to antibody enhancement (ADE) mediated by IgG, where, Dendritic Cells (DCs) ,which is found in respiratory tract, is considered as a link between innate and adaptive immunity, besides, it represents an important role as an Antigen Presenting Cells (APC). It is worthy to mention that, before MHC-I analysis it was noticed that protein sequence of SARS-COV-2 is introduced by alleles of HLA-C rather than HLA-A and HLA-B [9].

Moreover, it was found that HLA-B*46:01 had a small number of estimated SARS-CoV-2 binding peptides indicating that individuals with HLA-B*46:01 allele may be at risk of being attacked by COVID-19. On the other hand, it was reported that HLA-B*15:03 showed the highest extent to present a high conserved SARS-CoV-2 peptides that are possessed in common with another corona-viruses, which may promote cross-protective T-cell-based immunity [10].

From a research performed on about sixty-four Japanese patients, it was confirmed that there is an association of the specific HLA alleles and high risk of specific bacterial infection, in addition to the exacerbation of nodular bronchiectasis [11]. *In Addition, HLA-DQA1*05 alleles are reported to approach abundance in 40% of the European population, was shown to significantly increase the rate of anti-drug antibody formation.*

Patients carrying HLA-DQA1*05 alleles have shown anti-drug antibodies development when managed with adalimumab and infliximab, and for those treated using a mono-therapy or a combination therapy with immune-modulators. Moreover, it acts on reducing the previously mentioned drugs' efficacy and therapeutic actions being, an anti-tumor necrosis factor resulting in lack of success in disease management, and occurrence adverse drug reactions [12]. It was noticed that there was a lower prevalence of severe COVID-19 cases in patients managed with anti-TNF-α than those patients taking steroids [13].

One more study was conducted on Belgian and Canadian patients to explore the association of HLA polymorphism with abdominal aortic aneurysms and autoimmunity contribution in disease pathogenesis, where, the results showed that populations carrying HLA-DQA1 locus are at higher risk to develop this disease [14] It is worthy to mention that, a study was conducted on 1980 Italian and Spanish patients suffering from COVID-19 and respiratory failure showed absence of correlation or relationship of HLA alleles with incidence of (COVID-19) [15].

Conclusion

From this review it can be concluded that HLA-DQA1 may induce production of anti-drug antibody against anti-TNF drugs like infliximab, adalimumab; which are used as an options in management of COVID-19, and therefore might result in management failure. Also, HLA-B*46:01 carrier individuals are more vulnerable for COVID-19. Further investigations and researches is recommended to address the relation between HLA-DQA1 carrier population, and its potential effect on the COVID-19 patient response to recommended protocols.

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