Review Article

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Impact of genetics on predisposition and prognosis of COVID-19

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Abstract

The global pandemic of COVID-19 accounts for more than 3 million deaths globally. COVID-19 is a contagious infection caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Wide range of clinical manifestations from gastrointestinal (GI) symptoms, loss of smell and taste and mild and severe respiratory infection to death has been reported with COVID-19. However, not much is known about the role of genetics in predisposition and progression of COVID-19. It is assumed that immense diversity of symptoms in infected individuals may be due to differences in host genetic characteristics and that genetic variations may be involved in determining the outcome of disease. However, the exact underlying mechanisms of these variations is unknown to date. Profound understanding of the underlying factors such as host genetics that determine the degree of susceptibility to infection and the disease severity may assist in better prediction of the population with the highest risk of infection along with achieving better medical treatment. In this review, we focused on the play of genetic variants associated with the susceptibility and severity of COVID-19 disease in the recent pandemic.

Keywords: SARS-CoV-2, genetics, polymorphism

• Introduction

The COVID-19 pandemic has become a global threat this year, with heavy consequences and financial losses. COVID-19 is a contagious infection caused by the novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), with an enveloped, single, positive-stranded RNA genome. Wide range of clinical manifestations from gastrointestinal (GI) symptoms, loss of smell and taste and mild and severe respiratory infection to death has been reported with COVID-19. Unfortunately the severity of symptoms does not sometimes dependent to age or health conditions (1-3). Previously published data suggest that this range of symptoms in infected individuals may be due to differences in host genetic characteristics and that genetic variations is involved in determining the outcome of infection. However, the mechanisms of these variations is currently unknown. The exact understanding of the factors such as host genetics that determine the degree of susceptibility to infection and the disease severity in patients can help better predict the population with the highest risk of infection or find a new target for treatment interventions or vaccine production (4, 5). Therefore, investigation of the role of single nucleotide polymorphisms (SNPs) in specific COVID-19-related genes such as human leukocyte antigen (HLA), ABO gene, interferon-induced transmembrane protein 3 (IFITM3), angiotensin-converting enzyme 2 (ACE2), transmembrane protease serine-type 2 (TMPRSS2), and vitamin D binding protein (DBP) may provide clues in prediction of incidence and severity of COVID-19.

In this review, we summarized the genetic variants associated with the susceptibility and se-

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verity of COVID-19 disease due to the recent pandemic.

• Human leukocyte antigen (HLA)

Human leukocyte antigen (HLA) is an important host genetic factor which is located in the short arm of human chromosome 6. HLA is known as a regulator in various immunological functions, plays a pivotal role in the presentation of antigens to T lymphocytes and protection against microorganisms. Genetic variations on HLA gene is reported to be associated with infectious diseases (6). The HLA system is classified into three distinct classes of genes (classes I, II, and III), and protection against viral infections such as HIV has been reported to be linked to the polymorphisms in HLA class I (7, 8). Recent findings is suggestive of the association between HLA gene polymorphisms and risk of SARS-CoV-2 infection. The effect of HLA genetic polymorphisms on the recognition of SARS-CoV-2 antigen viral peptide epitope is mostly seen by class I antigens of HLA (A, -B, and -C), especially HLA-B*46:01. The individuals with the HLA-B*46:01 genotype experience a severe form of COVID-19, while those with the HLA-B*15:03 genotype, had the least susceptibility to increased disease severity (9, 10). On the other hand, in a recently published study an association between the alleles of HLA-A*11, HLA-C*01 and HLA-DQB1*04 and increased mortality rate in COVID-19 patients was observed (11). HLA-DRB1*08, one of the genetic polymorphisms of class II antigens of HLA, is more frequent in COVID-19 patients which increases the risk of mortality in these patients. Low affinity of this antigen for viral peptides and the consequent inability of the immune system to detect the virus has led to an increased mortality rate in Covid-19 patients carrying this variant (12).

• ABO blood groups

Based on several studies performed on the effects of the ABO variant in susceptibility to COVID-19 infection, higher risk for infection was reported in individuals with blood type A, and lowest risk was seen in patients with O blood type (13-15). The protective effect of blood type O against virus infection may be due to the expression of the antibodies against glycan antigens A (anti-A antibodies) in these individuals which have the ability to inhibit SARS-CoV-2 to bind to angiotensin converting enzyme 2 (ACE2) (16). On the other hand, the relationship between COVID-19 severity and anti-A antibody may also depend on the immunoglobulin subtype of antibodies, since the isotope of anti-A antibody in blood group O, which is an IgG, provides more protection than the anti-A antibody in blood group B, whose isotope is IgM (17, 18). Association of ABO polymorphism with the progression of COVID-19 disease may also be due to a mechanism other than antibody type as well. In a study of COVID-19 patients Ellinghaus et al. found that rs657152 SNP, located on chromosome 9q34.2 at the ABO locus, may predispose patients to elevated levels of interleukin-6 (IL-6) and an increased risk of deterioration due to COVID-19 (19). The elevated circulating IL-6 levels is a biomarker for COVD-19 severity (20). Cytokine storm is the extra release of pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α following a viral infection that contributes to lethal outcomes of COVID-19 patients (22). Therefore, induction of cytokine storm can somehow be associated with the polymorphism of the ABO system.

• Interferon-induced transmembrane protein 3 (IFITM3)

Interferon-induced transmembrane protein 3 (IFITM3) is an antiviral effector of the host immune system that is induced by IFN-I and restricts virus entry into the cytoplasm of host cells by impairing virus–host membrane fusion, so polymorphisms in this protein may affect the severity of the viral infection (21). Data in COVID-19 patients indicated the possibility of an association between the rs12252 C-allele, rs34481144 A-allele and rs6598045 A-allele genotypes of the gene IFITM3 with SARS-CoV-2 infection risk (22-24). While a global epidemiological study demonstrated a negative association between the C allele of IFITM3 rs12252 polymorphism and COVID-19 related death rate (25). The positive association of the G allele of rs12252 of IFITM3 with mortality rate has been also seen in patients with decreased serum levels of IFITM3 (26).

In the process of virus entry to the host

cells, SARS-CoV-2 viruses need an acid-dependent proteases to remove outer-capsid proteins, but if the dependence of SARS-CoV viruses on proteases decreases, they will no longer be sensitive to the IFITM protein. On the other hand, the surface expression of ACE2, the receptors of SARS-CoV-2, is not affected by the expression of IFITM (27). Eventually, any polymorphism that results in the production of a short, or unstable/inactivated IFITM3 protein reduces IFITM-induced viral protection and increases the likelihood of viral infection(28).

● Angiotensin Converting Enzyme 2 (ACE2)

Overexpression of ACE2, the main receptor of SARS-CoV-2 which facilitates viral entry by interacting with its S protein region, increases disease severity and higher susceptibility to COVID-19 (29). Resistance to COVID -19 in some rare variants of the ACE2 gene (K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, D509Y) which have low affinity to S protein suggests a protective role of these variant (30). A significant decrease in the severity of COVID-19 in individuals with K26R and I468V polymorphism with low affinity to S protein verifies these observations (31). on the other hand, a molecular docking study on the interaction of ACE2 with SARS-CoV-2 spike protein showed that 6 variants (I21T, A25T, K26R, E37K, T55A, E75G) of ACE2 have a higher affinity to the SARS-CoV-2 Spike protein receptor relative to the wild type ACE2 and 11 variants (I21V, E23K, K26E, T27A, E35K, S43R, Y50F, N51D, N58H, K68E, M82I) have a lower affinity(32).

rs4646114 (C>T), a frequent ACE2 SNP in African population, is identified as having binding sites for the nuclear factor of activated T cells (NF-AT1), a transcription factor. NF-AT1 is activated after viral infection following the activation of T cells and induces ACE2 transcription so thus intensifying the penetration and spread of COVID-19 (33, 34). Another SNPs, rs4646115(T>C) and rs536092258 (C>A), can enhance ACE2 expression, with a potential binding site for another transcription factor C-EBPb and the steroid nuclear receptor GR-α, respectively (34). C-EBPb promotes the expression of certain genes which play a role in inflammatory responses in the lung and the liver (34, 35). GR-α is basically a nuclear receptor but is traditionally considered a transcription factor being involved in the rapid degradation of mRNA called GR-mediated mRNA decay (GMD). GMD can regulate monocyte function by targeting the stability of CCL2 mRNA, which is required to induce chemo-attraction of monocytes (36, 37).

rs370596467 (T>C), a variant with high frequency in the Asian population can suppress ACE2 activation by decreasing transcription factor binding site for the transcription factors, such as X-box binding protein 1 (XBP-1) which increases transcription of ACE2 (34). ACE1 I/D polymorphism is associated with a reduced expression of ACE2 which might also be crucial in COVID-19 infection (38-40). Higher frequency of TT or AA genotypes of rs2285666, another polymorphism that elevates the expression of ACE2, among an Indian population, is associated with increased susceptibility to COVID-19 infection (41). In addition, the presence of the minor A allele within the rs2106806 variant and the minor T allele within the rs6629110 variant is associated with an increase in the risk of COVID-19 infection but the findings must be confirmed in larger studies(42).

● Transmembrane protease serine-type 2 (TMPRSS2)

Transmembrane protease serine-type 2 (TMPRSS2), is a cell-surface polymorphic protein in epithelium cells as bronchial epithelial cells which facilitates virus-cell membrane fusion and viral spread in the infected host by proteolytic cleaving in ACE2 and S protein of SARS-CoV-2 (43). Patients who carried delC allele (rs35074065) of TMPRSS2, which results in increased expression of both TMPRSS2 and MX1, are more susceptible to SARS-CoV-2 infection (44). It was observed that rs2070788 (G allele) and rs383510 (T allele) variants have also increased TMPRSS2 expression specially in lung tissue (45). Obviously, any variant in the TMPRSS2 gene that reduces its protein stability, such as the Val160Met (rs12329760), prevents viral entry and may provide different responses to COVID-19 (46). TMPRSS2 as a polymorphic gene had the highest correlated expres-

sion with ACE2 which were both sex dependent. The expression of TMPRSS2 in many male tissues is related to androgenic hormones and lack of its expression in female tissues explain higher rate and severity of infection in men (47). Considering that ACE2 is located on the X chromosome justifies the sex-dependent effect of ACE2 gene polymorphisms in men, besides in some studies ACE2 have had higher expression in men than women (47-49).

• Vitamin D related gene

Due to the association between vitamin D deficiency and the increased renin-angiotensin system (RAS) expression, and thereby increasing the risk of pneumonia, the role of vitamin D in preventing or reducing pulmonary symptoms in patients with COVID-19 becomes more prominent (50, 51).

Free vitamin D plays its role by binding to the vitamin D receptor (VDR) in the cell nucleus. The formation of the vitamin D/VDR complex leads to activation of vitamin D response elements in the genome and transcription of around thousand related genes (52). Polymorphism in VDR is closely related to the immunomodulatory effect of vitamin D, as it regulates the expression of Toll-like receptors (TLR), part of the innate immune system, that detect the presence of microorganisms (53, 54). The risk of acute respiratory infections is reported to be higher in healthy adults receiving vitamin D who have the minor alleles of rs4334089, rs11568820, and rs7970314 for VDR polymorphism (55). But so far no study on the risk of COVID-19 infections and VDR polymorphism has been reported. While the role of the vitamin D binding protein (DBP) gene polymorphism at rs7041 loci and the prevalence and mortality rate in infectious patients with COVID-19 has been researched and the results have shown that there was a positive significant correlation between hospitalization of COVID-19 patients and GT genotype in populations of China, Japan, Nigeria, and Kenya and TT genotype in populations of Germany, Mexico, Italy, Czech Republic, and Turkey. DBP is a polymorphic protein that is involved in transporting the active form of vitamin D produced in the liver to other organs in the body. Diverse affinities of different alleles of the DBP gene for vitamin D on one hand and the physiological effects of vitamin D in the lung on the other hand, explains the role of DBP polymorphisms in COVID-19 (56-59).

• Conclusion

In this review we focused on the role of polymorphisms of various genes affecting the course of COVID-19 in order to provide a venue for better predicting the actions of this disease. The study of the effect of host genetic variability in susceptibility and severity of COVID-19 can provide a better understanding of the pathogenesis of the virus and assist in smart therapy of the infected patients.

Conflict of Interest

None declared.

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