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Effect of Genetic Factors on COVID-19 Susceptibility and Severity: A Review

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Abstract

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a severe infection with respiratory and systemic manifestations. This infectious disease has a complex course and manifests itself with various clinical presentations, ranging from asymptomatic infection to a severe clinical course. These variations in severity have raised the question of whether the genetic or epigenetic variations have a role in COVID-19 susceptibility or severity, and that these factors can be used to predict the disease course. A whole-genome sequencing performed on 95 samples of SARS-CoV-2 identified 116 unique mutations, most of which were missense and synonymous. Moreover, some studies have reported a relationship between the COVID-19 severity and the genes ACE and TMPRSS2. The present review provides an overview of different genes that have been found to be implicated or related to the susceptibility to COVID-19 or its severity.

INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), which is caused by the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a severe infection with respiratory and systemic manifestations (1). As the third most aggressive coronavirus discovered, this virus was first identified in Wuhan, China, at the end of 2019. It belongs to the genus *Betacoronaviridae* and is more than 80% identical to the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), which caused it to be named SARS-CoV-2. On January 30, 2020, the World Health Organization (WHO) announced that the virus was a "public health emergency of international concern". Until April 1, 2020, a total number of 127,877,462 confirmed cases and 2,796,561 deaths due to the COVID-19 have been reported by the WHO (2).

This disease has a complex course and manifests itself with various clinical presentations, ranging from asymptomatic infection to a severe clinical course. It is a systemic disease that involves the cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic, and immune systems (4). Many risk factors have been identified that increase the susceptibility to infection and its severe course, including old age, male gender, specific races, obesity, hypertension, diabetes, and geographical region. The virus is delivered to the pulmonary epithelial cells through aerosols (4, 5). Various immune cells of the body can aggravate the inflammation. For example, peripheral neutrophilia and lymphocytopenia significantly intensify the immune response, causing several deleterious complications in the patients, including Acute Respiratory Distress Syndrome (ARDS), multi-organ dysfunction, and, subsequently, death. The recent introduction of safe and effective vaccines for COVID-19 is encouraging; however, the development of herd immunity and return to normal life are expected to be several months away (6).

These findings have raised the question of whether the genetic or epigenetic variations have a role in COVID-19 susceptibility or severity, and that these factors can be used to predict the disease course (7). Interpersonal, clinical variability is present in the course of any human infection, and COVID-19 is no exception. An extensive interpersonal variability has been observed in the clinical course of COVID-19. The disease ranges from asymptomatic or benign infection in more than 95% of the affected individuals to life-threatening pneumonia requiring intensive

care in less than 0.5% (8). Interpersonal variation in the susceptibility to COVID-19 is mostly due to the specific polymorphisms (variants) of several genes, especially those that code the host receptors involved in the viral entry process. These genetic alterations can be passed from one generation to the next and are detectable in at least 1% of the population. Therefore, such mechanisms can explain the interpersonal variations in the susceptibility to some mutagenic, complex diseases, such as COVID-19 (9).

The underlying mechanism of SARS-CoV-2 infection, and also SARS-CoV and another human respiratory coronavirus NL63, includes the binding of the virus to the membrane-bound form of the ACE2 receptor and subsequent internalization of the formed complex into the host cell. Therefore, it is hypothesized that some polymorphisms of the ACE2 gene can act as a genetic risk factor for COVID-19 (10). Apart from the role of the ACE2 receptor in the COVID-19, ACE2 is well-known for its role in hypertension. This review provides an update on the possible role of some specific genetic factors in the pathophysiology of COVID-19 (11).

CORONAVIRUSES

Coronaviruses are enveloped, single-stranded RNA viruses that cause respiratory, enteric, or cardiovascular diseases in humans and animals. There are hundreds of coronaviruses, most of which are specific to animals, such as pigs, camels, bats, and cats. Sometimes, these animal viruses infect a human, which is called a spillover event, leading to human infections (11). There are seven known types of human coronaviruses. Four of these viruses, KHU1, OC43, NL63, and 229E, cause mild to moderate respiratory infections, such as the common cold. However, the emergence of the other 3 viruses, SARS-CoV-2, SARS-CoV, and MERS-CoV, have demonstrated the importance of the Coronaviridae as emerging human pathogens. Both SARS and MERS have higher fatality rates than COVID-19; however, their human-to-human transmission rate is much lower. The SARS-CoV-2, which has ravaged across the globe in the past several months, has spread faster than influenza. It has been shown that an individuals infected with COVID-19 can spread the virus to 2 to 2.5 other persons, which can be compared with an influenza patient that can infect about 1.3 individuals (12, 13). Confirmation of the COVID-19 diagnosis can be done using a PCR test. The clinical diagnosis by physical examination and history-taking is difficult and cannot be trusted since many presentations of COVID-19 overlap with other illnesses. Moreover, a considerable number of patients are completely asymptomatic. The therapeutics for COVID-19 mainly include supportive treatment of the related signs and symptoms, and are designated to patients with more severe disease. For mild infection, the physicians usually prescribe over-the-counter medications, such as analgesics and antipyretics. More severe cases may require hospitalization and several treatments, such as steroids, oxygenation, or mechanical ventilation. There are also other treatments for COVID-19 in development. It has been suggested that IV monoclonal antibodies in early infection may alleviate the symptoms, severity, and duration of the disease (14).

GENETIC VARIATIONS IN SARS-COV-2

COVID-19 depends on several factors, including age, gender, specific races, healthcare quality, movement restrictions, self-isolation, and genetic and immunological variations (15). Apart from these, genetic variations of the virus can also affect pathogenicity and virulence. A number of studies have now looked at the genomic data to identify the new variants and find their relationship with disease severity. A whole-genome sequencing performed on 95 samples of SARS-CoV-2 identified 116 unique mutations, most of which were missense and synonymous. Emerging viral variants that can surpass the human immune system could be a challenge to researchers. Immune escape may cause a higher susceptibility of the previously affected individuals to reinfection and their lower responsiveness to vaccines (3, 15, 16).

ACE GENE (CHROMOSOME XP22.2)

The Angiotensin-Converting Enzyme (ACE) is responsible for converting angiotensin II to angiotensin I. This gene is expressed in most body organs, including the thyroid, lungs (bronchial tissue and alveolar cells type II), heart, esophagus, kidney, adipose tissue, liver, retina, vascular endothelium, small intestine, and nasal tissue (17). In addition to its role in hypertension, the ACE2 receptor is known as a host cell receptor contributing to the viral infection by coronaviruses. The SARS-CoV-2 attaches to the target cells through the ACE2 receptor. Therefore, this receptor facilitates the viral attachment, invasion, and penetration processes. ACE2 expression levels have been reported to be significantly increased in men than women, which can explain the male susceptibility to COVID-19 (18). ACE2 is a highly polymorphic gene, with about 1700 known polymorphisms with varying frequencies among different populations. Some of these polymorphisms are correlated with increased expression of ACE2 protein. These polymorphisms are more frequent in the East-Asian populations (19). pulmonary cells of individuals of different races showed that Asian males had a higher ACE2 expression than white and African individuals, suggesting their potential higher susceptibility to the viral infection (20).

WHAT IS THE ACE2 STRUCTURE AND FUNCTION?

Angiotensin-converting enzyme ,ACE2, is a zinc-containing metalloenzyme located on the membranous surfaces of intestinal enterocytes, renal tubular cells, and some other cells. ACE2 protein contains an M2 domain, a peptidase, at its N-terminal, as well as a collectrin domain at its C-terminal, which is a renal amino acid transporter. ACE2 is a single-pass type I membranous protein, with its enzymatically active domain exposed on the surfaces of intestinal cells and cells in other tissues. The extracellular domain of ACE2 is cleaved from the transmembranous domain by another enzyme named sheddase, and the resulting soluble protein is released into the circulation and is ultimately excreted in the urine (20, 21).

ACE2 has multiple roles, including catalytic activities for specific substrates, a negative regulator for the Renin-Angiotensin-Aldosterone System (RAAS), B0 AT1 amino acid transporter, and receptor for the mentioned coronaviruses. ACE2 receptor is extensively found in several tissues, including lungs, kidneys, heart, and testis. Low expression levels of ACE2 mRNA have been associated with hypertension and heart failure, while the reduced levels of cardiac ACE2 have been reported in hypertension and diabetic heart disease. These multiple physiological roles of ACE2 have been hijacked by SARS-CoV-2 to serve as a receptor, resulting in COVID-19 (22).

RELATIONSHIP BETWEEN ACE2 EXPRESSION AND COVID-19

In general, children with confirmed COVID-19 are mainly asymptomatic or have mild symptoms (23), while it has been shown that children usually have higher plasma levels of ACE2 than adults. Moreover, data regarding COVID-19-related mortality suggests that men are more susceptible to COVID-19 than women. Multiple reasons have been proposed for this intergender difference, including pregnancy, sex chromosomes, estrogen signaling, and ACE2 receptor levels. Thirty-two polymorphisms, including 7 hotspot mutations of Lys26Arg, Ile468Val, Ala627Val, Asn638Ser, Ser692- Pro, Asn720Asp, and Leu731Ile/Leu731Phe, have been identified for ACE2 in data from a project on 1000 genomes and the China Metabolic Analytics Project. Thus, genetic variations between different populations can also affect the ACE2 function. Overexpression of ACE2 receptor and the related two proteases have been associated with identified factors increasing the COVID-19 susceptibility and severity, including old age, male gender, and smoking (24). Also, some ACE2 polymorphisms (HGNC:13557) have been described that alter its transcriptional activity (e.g., rs2285666, c.439+4G>A). A recent study found higher frequencies of alleles associated with ACE2 overexpression (e.g., rs143695310) in the East Asian populations, suggesting the higher susceptibility to COVID-19 in these populations. Since characteristics of COVID-19 differ between geographical regions, age groups, and races, it is possible that the ACE2 polymorphism may affect the susceptibility or resistance to the virus. Identification of the frequent variants of ACE2 will aid in developing preventive measures against COVID-19. However, further documents are needed to establish the presence of a strong relationship between ACE2 gene variation and COVID-19 (25).

TMPRSS2 GENE

Another human receptor with an important role in the viral entry into the target cells is TMPRSS2. The analysis of TMPRSS2 expression in human tissues revealed its overexpression in the pulmonary tissue. This gene has 4 polymorphisms (rs464397, rs469390, rs2070788, and rs383510), which are believed to influence its expression and function. TMPRSS2 can cleave and activate the S protein of SARS-CoV-2 during membranous fusion. Moreover, this protease can cleave the SARS-CoV-2 receptor and the ACE2 carboxypeptidase, whose cleavage has been shown to facilitate the viral entry into the host cell (24, 25, 26). Therefore, TMPRSS2 can also help in SARS-CoV-2 entry into the host cells. In addition to pulmonary tissue, TMPRSS2 is also expressed in the cardiac endothelium, renal tissue, and gastrointestinal tissue, suggesting that these organs can be important targets for COVID-19. Given the expression of this gene in the microvascular endothelium, infection with SARS-CoV-2 may cause endothelial dysfunction, leading to thrombosis and associated complications. Thrombotic complications have been observed in patients with severe COVID-19, which can be explained by the role of TMPRSS2 in this viral infection. In addition, ACE2 needs to be processed for S-driven entry of SARS-CoV-2 through these proteases. TMPRSS2 increases this entry due to its competition with metalloprotease A, disintegrin, and metalloprotease 17 for ACE2 processing (27, 28).

VARIANTS IN POLYMORPHISMS OF OTHER GENES AND THEIR ASSOCIATIONS WITH COVID-19 SUSCEPTIBILITY

Induced Transmembrane Protein 3 (IFITM3) is an antiviral protein that prevents infection by blocking the entry of many viruses into the host cell. It inhibits the fusion of viruses to the cellular membrane by affecting the membrane's fluidity (29). Therefore, polymorphisms in this protein have been found to affect the susceptibility and severity of respiratory infections, such as influenza and COVID-19.

Another protein, DPP4, is a transmembranous glycoprotein and an ectopeptidase that cleaves amino-terminal dipeptides, causing T cell activation. This gene affects the immunoregulation of the

host cells, influencing viral infections (30). DPP4 accelerates pulmonary inflammation, resulting in fatal respiratory distress in MERS. Both SARS-CoV-2 and MERS-CoV infect the lower respiratory tract and can lead to ARDS, suggesting a relationship between SARS-CoV-2 and DPP4. Given these findings, DPP4 inhibitors, such as gliptins, were used in COVID-19 and could significantly reduce the viral proliferation and load, as well as reducing the possibility and severity of the cytokine storm and inflammation of the lower airway (30, 31).

The role of ABO in genetic and non-genetic studies have reported that ABO antigens affect the COVID-19 susceptibility and clinical manifestations. Previous reports and GWAS observed a higher risk of COVID-19 in individuals with blood group A than those with other blood groups, as well as a lower susceptibility for those with blood group O. ABO blood group has been previously reported to be associated with susceptibility to some other infections, such as influenza, malaria, schistosomiasis, and SARS-CoV (29).

DISCUSSION

The present review provides an overview of different genes that have been found to be implicated or related to the susceptibility to COVID-19 or its severity. The rapid spread and considerable mortality of COVID-19 have undoubtedly attracted global attention, posing a significant threat to public health. COVID-19 seems to be a multigenic and multifactorial disease with many genetic and environmental determinants (32). Identifying the factors implicated in the COVID-19 is the key to better understanding its etiology and physiopathological mechanisms. In addition, it can help predict the risk of COVID-19 development to help in the prevention (33). The present review showed that many different genes could act as coronavirus receptors on the cellular surface. Therefore, they can be associated with a higher risk of COVID-19. Adaptive mutations in the SARS-CoV-2 genome can lead to its potential empowerment to provide an increased virulence, transmissibility, and immune escape ability. Similarly, natural genetical polymorphisms of the host receptors can increase the susceptibility or resistance against evolving pathogenic SARS-CoV-2. Therefore, a deeper understanding of these variations is crucial for developing effective measures and solutions needed to manage the future outbreaks of SARS-CoV-2 (30, 34).

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