TMSJ
TURKISH MEDICAL STUDENT JOURNAL

Turk Med Stud J 2023;10(2):41-6
DOI: 10.4274/tmsj.galenos.2023.2023-1-1

REVIEW

THE ROLE OF HOST GENETIC POLYMORPHISMS ON CORONAVIRUS DISEASE 2019 PATHOGENESIS

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ABSTRACT

An agent that emerged with a series of pneumonia cases of unknown etiology in China in December 2019 and caused the coronavirus disease-2019 pandemic, has been defined as severe acute respiratory syndrome coronavirus 2 as a result of studies conducted in a group of patients presenting with cough, dyspnea, and pyrexia. Viral entry into host cells starts and affects critical steps of pathogenesis. This step includes host receptor-viral spike protein interaction and enzyme activity. Varying degrees of host responses to viral entry are observed among individuals. Polymorphisms, that may be detected in communities and attributed to host cells, have a role in the pathogenesis of coronavirus disease infection. The reason why this has been considered is that receptors, enzymes, and other physiological response mechanisms' structures are idiosyncratic. Genetic variants that aid spike 1 protein and angiotensin-converting enzyme 2 binding are associated with susceptibility to infection because it is easier for the viruses to enter cells. On the contrary, genetic variants that inhibit binding are related to better outcomes because it is harder for the virus to invade. The transmembrane protease serine gene is another region for genetic polymorphisms. When there is a genetic variant in the regulatory region two outcomes can occur: up-regulation or down-regulation. Since the transmembrane protease serine gene oversees viral entry, up-regulation or high expression of this gene causes worse outcomes. Specifically, the rs2285666 variant of the *angiotensin-converting enzyme 2* gene is found to decrease expression, making it protective, while the rs12329760 variant of the transmembrane serine protease gene makes patients more susceptible to worse consequences. Many other variants of genes are associated with coronavirus disease, but they require further careful investigation to understand the mechanism behind the relation. Human leukocyte antigen and AB0 blood group genes, vitamin metabolism genes, and others are found to have a role in coronavirus disease pathophysiology. This study aims to show most of the probable polymorphic sites of host cell genetics that may influence the pathogenesis of coronavirus disease.

Keywords: Angiotensin-converting enzyme 2, COVID-19, etiology, genetic polymorphism, SARS-CoV-2

INTRODUCTION

In December 2019, in Wuhan, China, the number of pneumonia cases presenting with cough, high temperature, and dyspnea suddenly increased. The etiologic agent has been identified as the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) as a result of studies conducted on groups of pneumonia patients (1). The coronavirus disease-2019 (COVID-19) pandemic, caused by the SARS-CoV-2 novel virus, was officially declared by the World Health Organization (1). After two and a half years of the outbreak, many vaccines were developed and applied to humans. Various variants of the virus have had different impacts on the public and health systems. The presentation of COVID-19 can vary from being completely asymptomatic to death. Commonly seen symptoms of the infection are pyrexia, dry cough, and fatigue (1). The disease is transmitted via respiratory droplets, mostly due to close contact (2). Studies showed that viral nucleic acid is found in patients' feces, urine, blood, serum, ocular secretions, and semen, however, it is not clear, yet that disease may be transmitted via these routes (2). Also, no information about sexual transmission is present (2). To confirm COVID-19 infection, a real-time quantitative polymerase chain reaction test is extensively used (3). Since the primary system affected by the virus is the respiratory system,

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Received: 06.01.2023 Accepted: 05.06.2023

Cite this article as: Şahin E, Dağ A, Eren F. The role of host genetic polymorphisms on coronavirus disease 2019 pathogenesis. Turk Med Stud J 2023;10(2):41-6.

nasopharyngeal swabs are used to detect viral nucleic acid (3). Non-specific markers of inflammation, such as C-reactive protein and erythrocyte sedimentation rate, are also useful for diagnosis (3). Radiological images show ground glass opacity, which is not pathognomonic of COVID-19 infection (4). Microscopic bilateral diffuse alveolar damage due to loss of both type 1 and type 2 pneumocytes with cellular fibromyxoid infiltrates and interstitial mononuclear inflammatory infiltrates with lymphocyte dominance is seen in patients (3, 4). When cases in China were studied, it showed that the mean incubation period of SARS-CoV-2 is 5-6 days (range 2-14 days) (5). The disease burden is not limited to the death toll and confirmed cases. It is extensively related to the economy, social activities, and education in the world (6, 7). Countries whose economies depend on factors that are affected by the global shock that the pandemic created are more susceptible to indirect losses (e.g., tourism) (8). Direct losses are due to illness and mortality (8). Countries get affected by the virus to different extents, just like individuals. One of the most important differences between individuals is genetics. Everyone has a unique genetic sequence that is inherited from their parents. Individuals might have genetic mutations sporadically (9). Some variants are more common than mutations and they are called polymorphisms (9). It is known that genetic polymorphisms have an important role in the binding of an agent to a host cell, the response of the host cell to the disease, and its susceptibility to the disease (9). This study aims to present the latest data about the effect of detected genetic polymorphisms on COVID-19 infection pathogenesis and prognosis.

Virology

Coronaviruses have four major structural protein-coding genes: Spike protein (S), envelope protein (E), membrane protein (M), and nucleocapsid protein (N) (10). As we know from literature, viral spike protein (S protein) uses the angiotensin-converting enzyme 2 *(ACE2)* receptor in human tissues (3). This makes tissues that have high *ACE2* expression susceptible to viral invasion. Coronaviruses have relatively large (~30 kb), single-stranded, and positive-sense genomes (3). We have encountered a variety of variants since the beginning of the coronavirus pandemic. Since humans are made of the same universal code as viruses, they are at risk to have genetic mutations. While some mutations are functional, some are not. These variants of the virus caused different outcomes, such as worse prognoses and enhanced contagiousness.

Pathogenesis Mechanisms and Possible Polymorphism Sites

Since genetic polymorphisms are alterations in the genetic sequence, structural and functional proteins which are encoded by these altered genes may be linked to overall diagnosis, prognosis, and sequelae of the disease. Not only proteins themselves but also mechanisms that are involved in the infectious process and immune response may be genetically polymorphic. Many sites in the human body are prone to being polymorphic because all levels of functionality are controlled on a genetic basis. When we started collecting data, we were faced with the fact that the most studied polymorphism in the human body is *ACE2* receptor polymorphisms regarding COVID-19 pathogenesis. *ACE2* receptor mutations are studied more in number when compared to other mutations regarding COVID-19 disease prognosis. Virus entry is possible via the *ACE2* receptor for both SARS-CoV-1 and SARS-CoV-2 (11). The virus binds to the *ACE2* receptor with its S protein (1). The S protein has two subunits, each with its distinct function. A complete spike protein consists of a trimer of S1-S2 subunits (12). The S1 subunit binds to the *ACE2* receptor via its receptor-binding domain (RBD), while the S2 subunit helps with the fusion (12, 13). Two processes are crucial for viral entry: binding of S1 to the *ACE2* receptor and S protein priming by host cell Transmembrane Protease Serine 2 *(TMPRSS2)* (14-16). Another process for the virus to enter a cell may be endosomal/lysosomal cysteine proteases cathepsin B and L (*CTSB*, *CTSL*) activity, however, it is not mandatory (14). Several studies stated that furin protease, cellular receptor neuropilin-1, and the *CD147* receptor are involved in SARS-CoV-2 disease infection as well (17-20). The *ACE2* receptor is the main receptor of the Renin-Angiotensin System (RAS) and its expression in cells is regulated by several pro and anti-inflammatory cytokines (21). RAS and opposing systems in the human body regulate the cardiovascular system, blood pressure control mechanism, neural and renal functions (21). *ACE2*, *TMPRSS2*, and *CTSB/L* genes are mostly expressed in kidney, heart, respiratory, gastrointestinal tract tissues, and even blood cells (21). Thus, the symptoms can be seen more readily in these systems and tracts that express the *ACE2* receptor due concentrated viral entry and proliferation (21). Still, tissues that have relatively low expression of the receptor have been affected via indirect mechanisms, such as the immune response of the host (21). The *ACE* receptor is found in healthy respiratory vascular endothelial cells, and therefore, a pathology in those cells may cause elevated serum *ACE* levels, as previous studies showed (22). The *ACE* genotype is considerably polymorphic, however, the extent of thoracic involvement is not found to be significantly related to the *ACE* receptor polymorphisms (22). According to recent studies, new hypotheses are posed for discussion. The relationship between the *ACE2* receptor and hypertensive drugs (*ACE* inhibitors) looks concerning to healthcare providers, and new research studies are being performed. According to the Council on Hypertension of the European Society of Cardiology, people on hypertension medication who use *ACE* inhibitors should continue using their drugs with no changes (23). Viral invasion of vascular endothelial cells, lung cells, and myocytes causes inflammatory changes such as edema, degeneration, and necrosis (3). Cardinal signs of inflammation may be seen. Thus, invasion starts an act on the body via pro-inflammatory cytokines. Interleukins (IL) such as IL-6 and IL-10, tumor necrosis factor (TNF)-α, granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein I, macrophage inflammatory protein 1α, programmed cell death protein I, T-cell immunoglobulin, and mucin domain 3 (Tim-3) are the main molecules that have a role in pathogenesis

(24). Increased release of pro-inflammatory cytokines is the etiology of cytokine storm and lymphocyte depletion (25). Degeneration of lungs, myocytes, endothelial cells, cardiac tissue, intestinal lining, and systemic effects experienced by the host are due to these circulating messenger molecules (24). Cardiopulmonary changes may cause a decrease in oxygen saturation, and eventually, cellular damage and cyanosis occur in distal parts of the body. Sensitive but not specific biomarkers are usually elevated, and troponin-T, natriuretic peptides, and IL-6 are prognostic factors related to poor results (3). Cardiac complications such as myocarditis, heart failure, and arrhythmias are among the causes of mortality. Gastrointestinal (GI) system-related symptoms are mainly nausea, vomiting, diarrhea, and abdominal pain (3). Hepatic injury is usually seen, which is detected by elevated enzyme levels of serum alanine aminotransferase, aspartate aminotransferases, bilirubin, and γ-glutamyl transferase (3). Hepatic injury is related to hepatotoxic medication, which can cause systemic inflammation, sepsis, respiratory distress syndrome-induced hypoxia, or multiple organ failure. Another system involved in the pathogenesis of COVID-19 is the nervous system (3). Symptoms are migraine, dizziness, seizure, decreased level of consciousness, acute hemorrhagic necrotizing encephalopathy, agitation, and confusion, accompanied by anosmia, hyposmia, and dysgeusia (3). Two important demographic prognostic factors are sex and age (26). After COVID-19 infection, developing severe complications is more common in men than women (26). As age increases hospitalization increases but not in a directly proportional manner: 0.1% in children and 10% or more in the elderly (26).

Complications of COVID-19 disease may be ordered as laryngeal edema and laryngitis, necrotizing pneumonia caused by a staphylococcal toxin (Panton-Valentine leukocidin), acute pericarditis, ventricular dysfunction, acute myocardial injury, arrhythmias, heart failure, acute respiratory failure, acute respiratory distress syndrome, ventilation-associated pneumonia, sepsis, multiple organ failure, and pulmonary embolism due to acute right-sided heart failure (3). When polymorphisms are studied in COVID-19 infection pathogenesis, it is seen that the *ACE2* receptor, *TMPRSS2*, and HLA are commonly studied polymorphism sites. Viral entry is mediated by the RBD surface network of polar contacts which are Lys417, Gly446, Tyr449, Asn487, Gln493, Gln498, Thr500, Asn501, Gly502, and Tyr505 (27). Variable susceptibility to COVID-19 infection and different outcomes can be explained by age, sex, and race differences between patient groups. When reviews are studied, it is inferred that the A*CE2* and *TMPRSS2* polymorphisms, male sex, and HLA-B*15:03 genotype are more vulnerable to COVID-19 (27). Male sex, old age, and the presence of comorbidities increase vulnerability (27). Both diabetes and hypertension are controlled by the *ACE2* receptor and are the most common comorbidities in COVID-19 patients (28). Because of various conditions, the *ACE2* receptor number decreases over time, and a deficiency of *ACE2* should favor disease progression (28). The *ACE2* receptor gene is located on the X chromosome (29). Males have higher expression of the gene and higher conversion of Angiotensin II than females (30). Therefore, it is concluded that female patients might have lower sensitivity to viral infection (30). In a study, two distinct DNA sequences were found linked to the decreased binding capacity of the S protein to the *ACE2* receptor, thus a favorable outcome and increased resistance to viral entry are reported (31). Also, some specific variants of the *ACE2* gene are found to be a factor in the reduction of expression. The rs2285666 variant of *ACE2* reduces the expression and thus might be protective against viral entry (31). In COVID-19 infection, excessive production of immune mediators causes a cytokine storm. The cells that have a role in the cytokine storm also express the *ACE2* receptor (32). There are many functional variants of the *ACE2* receptor gene that are related to increased binding affinity to the S protein. However, some functional variants are found to be linked to decreased affinity (33). Regulatory variants of the *ACE2* receptor gene increase the expression of the *ACE2* and *TMPRSS2* genes (33). It is found that 13 gene variants increase interaction between S1 and *ACE2*: H378R and S19P, European and African variants, respectively (34). In the same study, some other 18 single nucleotide polymorphisms were found to be related to inhibition of the interaction between S1 and *ACE2*: Q388 L and M82I, American and African variants, respectively (34). An association between the *TMPRSS2* p.Val160Met variant and COVID-19 infectivity has been identified in a study, but this study showed no correlation between increased polymorphism and the severity of disease (35). Another study showed that *TMPRSS2* deficiency reduces the severity of disease (36). Distinct variants were investigated, which showed that variants that highly expressed the gene were more susceptible to disease (36). East Asian populations have a lower frequency of genotypes that are associated with high expression compared with American and European populations (36). Studies revealed that the ABO system of blood groups may have an impact on disease pathogenesis (37-43). In chromosome location 9q34.2, there is a polymorphism known as rs657152 which causes a higher risk of infection for blood group A compared to non-A blood groups and a lower risk of infection for blood group O compared to non-O blood groups (37). A polymorphism (in 19q13.32, rs429358) that alters the gene sequence of Apolipoprotein E causes severe disease in patients with comorbidities such as dementia, diabetes, and cardiovascular disease (38). In the HLA loci, two polymorphisms are found to be associated with disease vulnerability and immunity: B*46:01 and B*15:03, respectively (39). A polymorphism (in the 11p15.5 location, rs12252) found in interferon-induced transmembrane protein 3 (IFITM3) is associated with mild-to-moderate disease (40, 41). Polymorphisms in the TLR7 and TMEM189-UBE2V1 genes were also associated with severe disease (37). Polymorphisms of the Interleukin-6 gene are associated with increased susceptibility to chronic obstructive pulmonary disease, pneumonia, various viral infections, and idiopathic pulmonary fibrosis among different populations via different variants (42). These diseases might present as co-morbidities in COVID-19-infected patients.

Co-morbid diseases also affect the progression and prognosis of the main course of the infection. Some polymorphisms might have an indirect effect, as mentioned above, via increasing the risk of probable co-morbid diseases.

A recent genome-wide association study reported that polymorphisms in the *SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1* genes were found to be related to severe respiratory failure (43). "Two polymorphisms, the rs11385942 insertion/deletion polymorphism of the leucine zipper transcription factor-like protein 1 (LZTFL1) gene and the rs657152 SNP of the *ABO* gene, are related to severe COVID-19 cases with respiratory failure" (43). The gene responsible for producing methylenetetrahydrofolate reductase *(MTHFR)* is polymorphic among Latinx populations (44). The number of people carrying the MTHFR 677 T-allele is found to be high in this group, as is the mortality from COVID-19 infection (44). Thus, a strong correlation between the C677T variant and mortality from COVID-19 infection was found (44). It is seen that 8 genetic polymorphisms are associated with COVID-19 mortality. These genetic variants were seen on chromosomes 2, 6, 7, 8, 10, 16, and 17 (45). Genes related to ciliary dysfunction (*DNAH7* and *CLUAP1*), cardiovascular diseases (DES and SPEG), thromboembolic disease (*STXBP5*), mitochondrial dysfunction (*TOMM7*), and the innate immune system (WSB1) were found to be related to susceptibility to severe disease (45). *DNAH7* was found to be the most down-regulated gene in COVID-19 infection of bronchial epithelia (45). In a study conducted by Turkish researchers, it was hypothesized that vitamin D binding protein (DBP) polymorphisms might affect COVID-19 infection (46). DBP is known as the most polymorphic protein (46). DBP affects biological functions. Polymorphism of this protein gene is associated with susceptibility to different diseases such as Hepatitis C and metabolic syndrome (46). It was hypothesized that this highly polymorphic gene may be associated with COVID-19 infection. As the result of the study, they found that there is a significant positive "correlation between the prevalence and mortality rates and the GT genotype, while there is a significant negative correlation between the prevalence and mortality rates and the TT genotype at the rs7041 locus among all populations" (China, Japan, Nigeria, Kenya, Mexico, Italy, Türkiye, Finland, Germany, Czech Republic) (46). A relationship is found between the *OAS1* (oligoadenylate synthetase 1) gene variations and Alzheimer's and COVID-19 (47). The single nucleotide polymorphisms rs1131454 (A) and rs4766676 (T) are associated with Alzheimer's disease while rs10735079 (A) and rs6489867 (T) are associated with severe COVID-19 (47). *OAS1* is found to be functional in limiting the pro-inflammatory response of myeloid cells (47). A decrease in *OAS1* gene expression should increase the susceptibility to cytokine storm (47). It is found that the GG genotype of the patatin-like phospholipase domain-containing protein 3 (*PNPLA3*) (*rs738409 locus*) gene is associated with a severe outcome when sex influence is adjusted (27). Also, the same genotype was found linked to being more vulnerable to tissue damage in cases of inflammation and up-regulation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome. However, in the same study, no association between the interferon (IFN) lambda system and the outcome of COVID-19 was detected. Previous studies revealed that the IFN lambda system may be associated with reduced viral clearance in African children with coronavirus and rhinovirus infections (27). In the infection state, the lung parenchyma is extensively infiltrated with macrophages and T helper cells (27). Mer tyrosine kinase (MERTK) is a receptor for macrophage subpopulation M2 (27). In this study, it was found that MERTK polymorphisms do not affect patients in terms of the severity of the outcome (27). Other different studies suggest that the *PNPLA3-rs738409* polymorphism might be protective against severe COVID-19 disease (48-50). Although these studies suggest a protective effect, the *PNPLA3-rs738409* variant has been found to have a higher risk for severe disease, as mentioned earlier (27). Overall, it is difficult to understand how exactly this polymorphism alters disease pathogenesis and further studies are warranted (51).

Study Limitations

The subject of this study is a novel topic that needs further analysis of samples taken from COVID-19-infected patients of different groups in populations. Limited information about DNA polymorphisms causes restricted treatment options. Personalized medicine needs to know the differences among human populations to provide more effective treatment. Experimental clinical studies may obtain more data among world populations to determine which polymorphisms cause severe disease and which do not. Not only for COVID-19 disease but other diseases are thought to be related to genetic variants and heritage. It is incontrovertible to say that most diseases have a genetic background and that severity may be affected by environmental exposures. This study is also devoid of articles that we had to pay for to be able to read. With appropriate funding, more studies can be examined, and more extensive research can be done.

CONCLUSION

Gene polymorphisms and mutations may play a role in disease progression and sequelae. A novel virus, SARS-CoV-2 is one of them. Diseases should be investigated thoroughly to not miss any factors that might contribute to the pathogenesis and prognosis. This is possible via scientiface2 studies. In this study, we aimed to determine whether genetic polymorphisms affect COVID-19 disease pathogenesis and prognosis. It was concluded that genetic polymorphisms among human populations are associated with COVID-19 disease, and they partly determine disease outcome and severity via both direct and indirect mechanisms during the disease state. Most common polymorphisms are attributed to the *ACE2* gene because of its essential role in viral entry mechanisms. Genetic variants that aid the S1 protein and ACE2 binding may be associated with susceptibility to infection because it is easier for viruses to enter cells. On the contrary, genetic variants which inhibit binding are related to better outcomes. The another gene encoding TMPRSS2 is highly polymorphic. When there is a

genetic difference in the regulatory gene region, two outcomes can occur: up-regulation or down-regulation. Since *TMPRSS2* oversees viral entry, up-regulation or high expression of this gene may cause worse outcomes. Other polymorphic sites and variants among ancestry groups and smaller populations need further clinical experimental studies to gather more data for understanding the reality behind disease pathogenesis. One should never dismiss the concept of having comorbidities and underlying causes of the apparent disease state. Nevertheless, while the variant increases the main course of the disease, there might be factors that aid patients in healing.

Ethics Committee Approval: *N/A*

Informed Consent: *N/A*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Concept: E.Ş., A.D., F.E., Design: E.Ş., A.D., F.E., Data Collection and/or Processing: E.Ş., A.D., Analysis and/or Interpretation: E.Ş., A.D., F.E., Literature Search: E.Ş., A.D., F.E., Writing: E.Ş., A.D., F.E.*

Financial Disclosure: *The authors declared that this study received no financial support.*

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