The Impact of ACE2 Gene Polymorphism in the Development of COVID-19 Disease

COVID-19 Hastalığının Gelişiminde ACE2 Gen Polimorfizminin Etkisi

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ABSTRACT

Coronavirus disease 2019 (COVI-19) was first reported in December, 2019 and virus caused COVID-19 have rapidly spread all over world. Transmission occurs very easily via droplet, aerosol and contact, so mask, hygiene and social distance are important protective factors. Some subjects showed severe findings when some subjects develop disease without any symptoms, so responses to disease differ individually. Genetic structure of subjects may be responsible for different responses. Angiotensin converting enzyme 2 is a polymorphic enzyme and has a crucial role for viral entry. Virus called Severe Acute Respiratory Disease (SARS) Cov-2 uses ACE2 receptor as a substrate to enter into host cells so it is considered that *ACE2* gene polymorphism may be responsible for different response to disease. In this study, the distribution of *ACE2* gene polymorphism and infected cases were presented in 6 populations all over the world and the related evaluations were made. It has been observed that *ACE2* gene polymorphism is protective against the development of COVID-19 disease in Africa and Eastern Mediterranean populations. However, there was no any association between *ACE2* gene polymorphism and the number of infected cases in American and European populations. Cytokines are important immune system parameters since they cause cytokine storm. Not only *ACE2* gene polymorphisms but also cytokine gene polymorphisms should be investigated for subjects' different responses to COVID-19 disease. Studies should be made to find out responsible factor for these different responses to disease, the associations between gene polymorphisms of other proteins on immune system and development of COVID-19 disease.

Key Words: COVID-19, *ACE2* gene polymorphism, infected cases, disease development

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ÖZET

Corona virus hastalığı ilk kez Aralık 2019'da rapor edilmiştir ve virüsün neden olduğu COVID-19 tüm Dünyada hızlıca yayılmıştır. Bulaşma damlacık, aerosol ve temasla kolayca meydana geldiği için maske, hijyen ve sosyal mesafe önemli koruyucu faktörlerdir. Bazı bireyler hastalık çok ciddi bulgularla seyrederken bazı bireylerde herhangi semptom vermeden gerçekleşmektedir yani hastalığa cevap bireysel olarak farklılık göstermektedir. Bireylerin genetic yapısı bu farklılıktan sorumlu olabilir. Anjiotensin dönüştürücü enzim 2 polimorfik bir enzimdir ve viral girişte kritik role sahiptir. Şiddetli Akut Solunum Yolu Hastalığı (SARS) Cov-2 adı verilen virüs, konakçı hücrelere girmek için substrat olarak ACE2 reseptörünü kullanır, bu nedenle ACE2 gen polimorfizminin hastalığa karşı farklı yanıtlardan alınmasından sorumlu olabileceği düşünülmektedir. Bu çalışmada ACE2 gen polimorfizmi ve enfekte vakaların dağılımı tüm dünyadaki 6 popülasyonda sunulmuş ve ilgili değerlendirmeler yapılmıştır. ACE2 gen polimorfizminin Afrika ve Doğu Akdeniz popülasyonlarında COVID-19 hastalığının gelişmesine karşı koruyucu olduğu görülmüştür. Bununla birlikte, ACE2 gen polimorfizmi ile Amerikan ve Avrupa popülasyonlarındaki enfekte vaka sayısı arasında herhangi bir ilişki yoktu. Sitokinler, sitokin fırtınasına neden oldukları için önemli bağışıklık sistemi parametreleridir. Sadece ACE2 gen polimorfizmleri değil, aynı zamanda sitokin gen polimorfizmleri de bireylerin COVID-19 hastalığına farklı yanıtları için araştırılmalıdır. Hastalığa verilen bu farklı yanıtlardan sorumlu faktörü, bağışıklık sistemi üzerindeki diğer proteinlerin gen polimorfizmleri arasındaki ilişkileri ve COVID-19 hastalığının gelişimini ortaya çıkarmak için daha fazla çalışma yapılmalıdır.

Anahtar Sözcükler: COVID-19, ACE2 gen polimorfizmi, enfekte vakalar, hastalık gelişimi

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INTRODUCTION

Coronavirus disease 2019 was first reported in Wuhan, China, in December 2019. Before COVID-19 pandemic, Severe Acute Respiratory Disease (SARS) and Middle East Respiratory Syndrome coronavirus (MERS-CoV) epidemics were experienced. All these epidemics has had spread around the world and become serious health concerns and also brought economic problems (1). This novel pathogen virus is responsible for the infectious respiratory disease called Covid-19 (Coronavirus Disease 2019). When this virus first appeared, we did not have any information, but as the data were obtained from SARS and MERS our knowledge about this new virus have been increased, but it still carries unknowns. There are currently no drugs, vaccines or any medical interventions to treat the disease caused by this virus.

All above 3 coronaviruses belong to the Coronaviridae family. Corona viruses are subdivided into 4 genera namely α-, β-, γ-, and δ- CoV (2). The name of SARS-CoV-2 was suggested by the International Committee on Taxonomy of Viruses since the receptor-binding gene region is similar to that of the SARS-CoV and also the virus uses the same receptor with that of SARS-CoV. SARS-CoV-2 is an enveloped, non-segmented, positive sense RNA virus (3). It is important to recognize virus by identifying it and furthermore receptor recognition is key issue for infectivity ability (viral entrance) and pathogenesis of virus. It helps to show a major target for vaccination and improve the antiviral strategy to cure disease or discover therapy. Virus uses angiotensin converting enzyme 2 (ACE2) protein as a substrate to entry the host cell (human body). Spike protein of virus mediates the entrance of virus into host cells (such as in type II pneumocytes in the lungs) (4). The protein, TMPRSS2, contains special region therefore, it specifically recognizes ACE2. Virus uses the ACE2 protein to enter the body, just like the SARS does, as a receptor since SARS-CoV-2 has a similar spike protein as SARS (Figure 1). There are 2 important regions, which provide an efficient binding between virus and ACE2, on the surface of virus. Some naturally selected mutations on the TMPRSS2 affect infectivity, pathogenesis, and transmissions of SARS-CoV (among different species and humans) (5). Virus membrane and host cells fuses and also, activation of some proteins cause the conformational changes in some proteins and all these changes allow virus to enter cells (6). Cells through the respiratory region, such as nasal epithelial cells, goblet cells and ciliated cells, after the entrance of virus, demonstrate high ACE2 expression. Furthermore, virus releases own genomic material (RNA) in the cytoplasm and then to the nuclei. Virus RNA is replicated for thousand times.

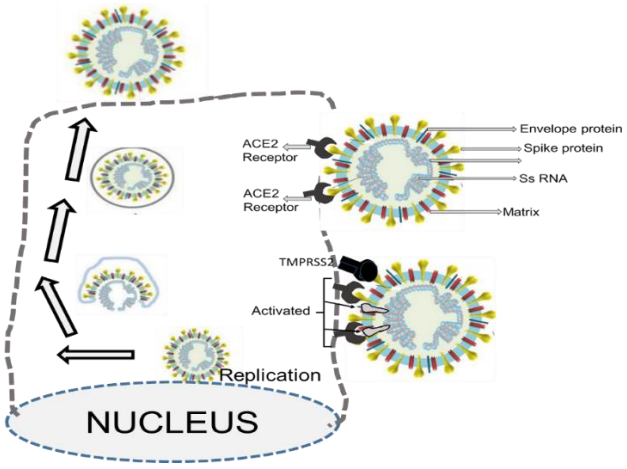

Figure 1. The entrance of SARS CoV-2 with relation to the ACE2

Hofmann et al. (7) and Li et al. (8) showed the positive correlation of ACE2 expression with Severe Acute Respiratory Syndrome (SARS-CoV) in *vitro*. As mentioned above, S protein of virus and other proteins such as TMPRSS2 are important proteins for viral entry. These 2 previously published studies demonstrated *in vitro* that a number of ACE2 variants could reduce the association ACE2 receptor with S-protein in SARS-CoV (7, 8). Therefore, the expression level and expression pattern of ACE2 are altered and different patterns belonging ACE2 are observed in different tissues. For this reason, this data might be critical in the susceptibility to COVID-19 and symptoms and outcomes of infection (9).

In some cases, disease develops asymptomatically (no symptoms) and some cases are affected seriously and they are critical cases and death take place. The reason for individuals to respond differently to the virus can be explained by genetic polymorphism. Different responses to the virus is considered to occur due to the genetic polymorphisms on *ACE2*. ACE2 is critical receptor for viral entry and infectivity of virus (10). Genetic polymorphism can alter the function of receptor and binding ability. All these changes may impact on virus infectivity (11). Rigat et al. (12) first showed that the Angiotensin I-converting enzyme (ACE) protein was polymorphic. ACE is responsible for the conversion of angiotensin I into angiotensin II. This conversion causes or mediates vital functions in the body such as blood pressure regulation and fluid and electrolyte homeostasis (13). This genetic polymorphism was important since it has an essential role in the genetic control of the levels of plasma ACE. Plasma ACE levels are varied among subjects which means that genetic differences are available since there is no any drastic change observed on the same subject (14).

Genetic polymorphisms have impact on the levels of ACE2. The units for ACE levels may differ from lab to lab according to methods applied such as μg/L for radioimmunoassay, or U/L for spectrophotometric detections (15). Furthermore, differences in units also depends on the age of healthy adult subjects (8-52 U/L) in normal conditions, of course, the average levels would change according to some diseases. ACE2 levels can also be low when you receive an ACE inhibitor drug, such as captopril or enalapril. All these parameters are taken into account while evaluating ACE2 levels.

Variations in DNA sequence contribute to individual differences. Not only individually differences but also differences among populations are important to be known, especially in the development of some diseases, such as *ACE2* gene polymorphism-cardiovascular disease relation (16). Specific genetic variation among populations contributes appreciably to differences in gene expression phenotypes. Therefore, it is important to determine the distribution of genotype or the frequencies of alleles of *ACE2* in different populations. Another crucial issue is that, if plasma ACE2 levels do not show the intrafamilial changes, similar levels are observed among family members, suggesting that there is a major gene which controls and affects the plasma levels of ACE2 (17).

The *ACE* gene is located on the chromosome 17q23 and it encodes ACE which plays a role in converting Angiotensin I into Angiotensin II. One of the well-known polymorphisms in the *ACE* gene is the *I/D* polymorphism, which "I" is from "*insertion*" of a base pair and "D" is from "*deletion*" of a base pair (the presence or absence of a 287 base pair) in intron 16. *I/D* gene polymorphism results in three genotypes (*II, ID*, and *DD*) (18). These genotypes have been shown to be associated with ACE activity and levels in plasma and tissues. Many studies have been showed that there is an association between genetic factors and disease susceptibility (19-21). In the case of *I/D* gene polymorphism, the serum ACE activity is higher in patients with sarcoidosis, which is an inflammatory disease, compared to healthy controls (22), since epithelioid cells, especially, sarcoid granulomas produce ACE, and also serum ACE levels are increased in patients with sarcoidosis (23).

Montgomery et al. (24) conducted a published study in Lancet journal on athletes to investigate the response to physical training. They found a positive correlation between the levels of ACE in human athletes' bloods and genetic polymorphism of *ACE* (24). This polymorphism has an important effect on the activity of ACE in plasma with about 50% change in ACE activity. This suggests that *ACE* gene polymorphism is very important and this data can be used for diagnosis, evaluation and treatment of some diseases.

The outbreak of the COVID-19 pandemic shows a marked geographical variation in its prevalence and mortality. Figure 1 shows that geographical distribution of COVID-19 regarding number of cases in the world based on World Health Organization (WHO) data (25).

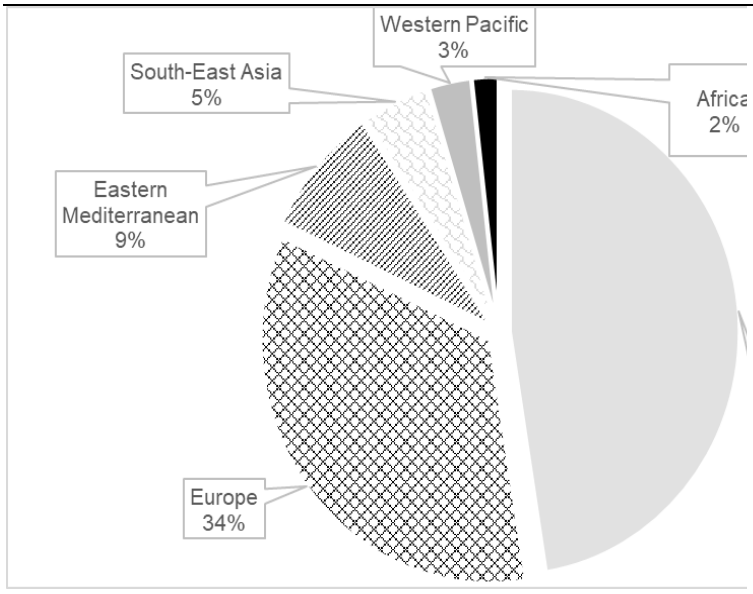

Figure 2. The geographical distribution of COVID-19 regarding number of infected cases in the World.

According to the geographical distribution of the case rates, America has the highest number of cases (47%) followed by Europe (34%). The lowest number of cases with 2% is observed in Africa. Not only *ACE2* is responsible for this difference in case distribution, but gene polymorphisms in cytokines may be responsible for this difference because cytokine storm which is characterized by excessive release of cytokines causes deaths in serious cases.

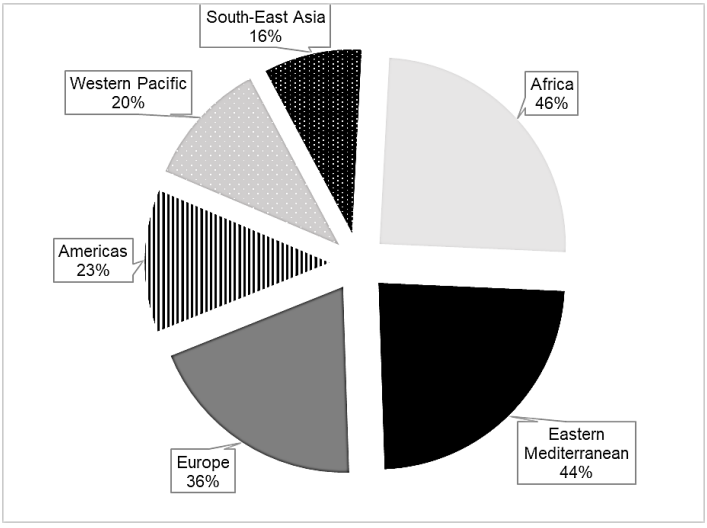

Figure 3. The geographical distribution of *ACE2 DD* genotype (%) in the world.

The *ACE I/D* polymorphism has been linked plasma ACE levels and moreover different functions; for example, the *DD* genotype is associated with the high levels of plasma ACE (26, 27).

Saab et al. (28) identified literature, between 1984 and 2006 reporting ACE I/D gene polymorphism to show geographically distribution of this polymorphism and they excluded the studies of a small sample size (<48) and subjects with unknown origin and having any disease. According to a meta-analysis of 145 studies with 49959 subjects, the overall prevalence of the *D* allele was 54.0%. The *II*, *ID* and *DD* genotype frequencies were 22.5%, 47.0% and 30.5% (28). Ethnicity was a major determinant of the *D* and *I* allele frequencies as the prevalence of the *D* allele was 39.1% in Asians, 56.2% in Caucasians and 60.3% in blacks (29). In the present meta-analysis study, the *D* allele had a frequency of 73.42% (28).

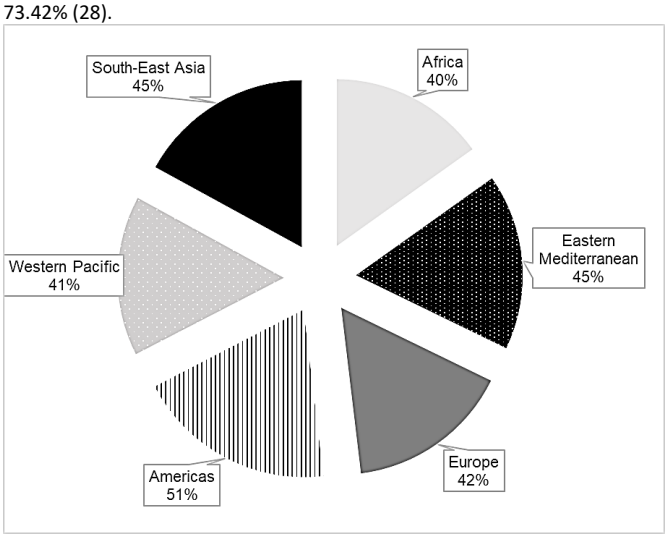

Figure 4. The geographical distribution of *ACE2 ID* genotype (%) in the world.

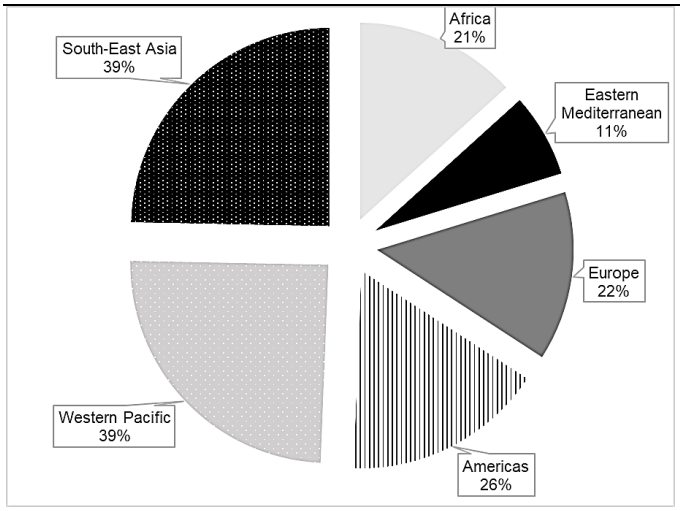

Figure 5. The geographical distribution of *ACE2 II* genotype (%) in the world.

Table 1. Genotype distribution of *ACE2 I/D* gene polymorphism according to the populations.

Population	*DD* (%)	*ID* (%)	*II* (%)
Africa	46%	40%	21%
Eastern Mediterranean	44%	45%	11%
Europe	36%	42%	22%
America	23%	51%	26%
Western Pacific	20%	41%	39%
South-East Asia	16%	45%	39%

Figures 3, 4 and 5 show *ACE2* genotype distributions according to geographic regions. WHO recorded infected cases and mortality rates by this geographic distribution. Considering this distribution, we created Table 1 by searching the studies in the PubMed database to find out *ACE I/D* genotype distribution. It is difficult to judge which genotype is responsible for the disease, since a reasonable relationship is not observed between the number of cases and the *ACE2* genotypes. According to the populations, the number of samples in the data related to the *ACE2* genotype distribution can be an effective factor. *II* % genotypes in Africa and Eastern Mediterranean populations are 21% and 11%, respectively.

CONCLUSION

These results suggest that *II* genotype is protective against to COVID-19 in Africa and Eastern Mediterranean population since the number of cases and mortality rates are low in these populations. No relationship is observed between the number of infected cases in other populations, including American and European populations, and *ACE2* gene polymorphism. Table 1 shows that the high number of infected cases and mortality rates in America and Europe cannot be attributed to *ACE2 I/D* genotype distribution. Since cytokines are important immune system parameters; not only *ACE2* gene polymorphisms but also other cytokine gene polymorphisms should be investigated. Future studies should be made to find out the possible associations between gene polymorphisms and COVID-19 disease.

Conflict of interest

No conflict of interest was declared by the authors.

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