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ACE2 Gene Polymorphisms Associated with COVID-19 Infection Susceptibility to Cardiovascular Disease

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Abstract

COVID-19, caused by SARS-CoV-2, was an emerging pandemic in December 2019 and was first reported by officials in Wuhan City, China. The Angiotensin-Converting Enzyme 2 (*ACE2*) is the main host cell receptor of human pathogenic SARS-CoV-2 and it plays a crucial role in the entry of the virus into the cell to cause and finally COVID-19 infection. We review the possible association of *ACE2* gene polymorphisms in COVID-19 along with the risk of cardiovascular disease. From the year 2020 onwards number of researchers reported *ACE2* main functional role in simulations has indicated several of these polymorphisms could affect interactions of SARS-CoV-2 and explained the concept of partial explanation for the regional differences and the disease severity. Here, we discuss the potential effect of polymorphisms of the *ACE2* gene in the main function of plasma *ACE2* activity in myocardial infarction, ischemic heart disease, and hypertension. Furthermore, we speculate on the potential role of *ACE2* gene polymorphisms of rs2285666 as a common genetic locus and susceptibility marker for the COVID-19 infection that might be associated with cardiovascular disease risk.

Keywords: *ACE2* polymorphism; Cardiovascular risk; COVID-19; Genetic susceptibility

Introduction

Critical pathways for hypertension control and kidney functions are attributed to Angiotensin-Converting Enzyme (*ACE*). *ACE-2* is one of the members of the *ACE* family protease and is attached to the cell membrane of (mACE2) in the kidney, heart, intestines, testis, and a soluble form in gallbladder (sACE2) [1,2]. The sACE2 lowers blood pressure by catalyzing the hydrolysis of angiotensin II into angiotensin [1-7]. Which in turn binds to MasR receptors creating the vasodilation and decreasing the blood pressure [7]? Cardiovascular and hypertension patients are mostly affected by blood pressure and making the entire processes a promising drug target [8]. The severe acute respiratory syndrome coronavirus 2, which was first discovered in December 2019, has subsequently, spread rapidly through global trade and travels [9]. The Coronaviruses (CoVs) are positive-sense single-stranded RNA, with the capacity to environmentally get rapidly mutated and recombination. COVID-19 is well-known to cause human respiratory and intestinal infections. The risk of serious illness of COVID-19 is mostly affected by older aged people, cardiovascular disease, diabetes, chronic respiratory disease, and cancer patients. Globally, in May 2021, there have been 51,39,55,910 confirmed cases of COVID-19, including 62,49,700 deaths, as reported by WHO. (WHO, COVID-19 daily reports, April-2022) [10]. The SARS-CoV-2 has affected humans and worldwide deaths ratio of 4.5 million [11]. In India, as on May 2022, a total of 4,30,94,938 confirmed positive cases of COVID-19 with 5,24,002 deaths as reported by WHO (WHO, May 2022) [12]. The review work was planned to investigate the high-risk genetic variants of *ACE2* gene SNPs in COVID-19 infection and their association with Cardiovascular Diseases (CVD). COVID-19 is discovered in December-2019, however, before the COVID-19 infection, *ACE2* gene polymorphisms were identified as susceptibility molecules in CVD. A recently higher number of new genetic variants were identified in the *ACE2* gene as the reason for COVID-19 infection. The cured COVID-19 infected persons with *ACE2* polymorphisms are at a higher risk of cardiovascular disease.

Methods

An extensive search was performed for literature collection from the *ACE2* gene polymorphisms in COVID-19 and cardiovascular disease utilizing PubMed, and other scholarly search bibliographic

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databases with a variety of terms that included, rennin-angiotensin system, pulmonary hypertension, and rs2285666 susceptibility in COVID-19 or cardiovascular disease.

ACE2 Gene Structure and Function

Activation of the Renin–Angiotensin System (RAS) plays an important role in the development and progression of cardiovascular complications. One of the pivotal components of renin-angiotensin system is *ACE*, which mediates various systemic and local regulations in the cardiovascular system and kidney and blockade of the RAS by Angiotensin-Converting Enzyme (*ACE*) inhibitors and Angiotensin (Ang) II receptor blockers have been shown to reduce Blood Pressure (BP) and the cardiac and renal complications of diabetes. The *ACE* exists in two isoforms, a somatic *ACE*, and testis-specific *ACE* (tACE). In 2000, two independent research groups discovered *ACE2*, one of the *ACE* family metalloprotease, unlike *ACE*, *ACE2* removes the carboxy-terminal phenylalanine in Ang-II to form the heptapeptide angiotensin-(1–7) [13,14]. The chromosome location of the *ACE2* gene is at Xp22 and the size is 39.98 kb, containing 18 exons and 20 introns [7]. The *ACE2* is identified as a functional receptor for the SARS Coronavirus (SARS-CoV) [8,15]. Serves as a main entry point in to the cell for coronaviruses such as HCoV-NL63, SARS-CoV, and SARS-CoV-2 [16,17]. *ACE2* is expressed specifically in heart and kidney and capable of cleaving Ang I and Ang-II into angiotensin 1-7 and angiotensin 1-9 respectively and other key vasoactive peptides, thus provides additional possibilities for the development of novel therapeutics [13].

The *ACE2* Gene Role in COVID-19

The *ACE2* contributes a central role in cardiac pathophysiology. Original SARS-CoV give rise to SARS-CoV-2 which differs from the original by 380 amino acid substitutions, and renders a difference in the receptor-binding domain between the viral spike (S) protein with surface expressed human *ACE2* [18]. This viral spike protein is target for therapeutic and vaccine development. The viral spike glycoprotein, synthesized as an inactive protein, is cleaved by the furin protease plasmin at furin cleavage site of spike protein, which is absent in SARS-CoV, thereby enhancing and increasing the cellular uptake of viral particles [19] by membrane fusion. Once the virus enter in to the host cell, the viral RNA is released and the host cell's cellular programs are utilized for viral replication of the host. The viral mediators down regulates *ACE2* and induce the ADAM Metallopeptidase domain 17 (ADAM-17) [20,21], latter cleaves *ACE2*, and directly pointing towards its direct involvement in COVID-19 and the RAAS system. Silhol et al. [22] proposed low *ACE2* level and a decrease in angiotensin 1–9 were correlated with a poor prognosis in acute respiratory distress syndrome. Similarly, COVID-19 viral mediated down regulation of *ACE2* and its product can also be correlated with a poor prognosis in COVID-19 [22].

ACE2 Gene Polymorphisms as a Risk in Cardiovascular Disease

CVD is the leading cause of mortality ratio in worldwide, representing 32% and 17.9 million people died in 2019, WHO, June, 2021 [11]. China had the highest number of heart disease deaths in 2018, followed by accounts in India, Russia, the United States, and Indonesia (Robert Preidt, Health Day Reporter, WEDNESDAY, December 10th, 2020 (Health Day News) [23]. It has been reported that COVID-19 can cause heart injury, even in people without underlying heart issues. The most frequently reported cardiovascular malfunction in COVID-19 is acute cardiac injury and it occurred in ~8% to 12% of all COVID patients. A unique interplay between SARS-CoV-2 and CVDs has been reported. Patel et al. reported that genetic variation of *ACE2* is associated in Caucasians with diabetic hypertension [24]. Lu et al. reported the *ACE2* gene G8790A variants are more significantly associated with essential hypertension in Chinese patients [25]. These studies demonstrate that the A allele of the rs2285666 polymorphism in the *ACE2* gene influences the risk of fatal CVD events to be a potential risk factor for males and females [26-31]. Cheng et al. [32] reported the *ACE2* SNP rs879922 may be common genetic loci and genetic susceptibility marker for T2D and T2D-related cardiovascular risks in Uygurs [32]. The SNP rs2285666 in *ACE2* has been reported as a risk factor for hypertension and heart failure [33-35]. Table 1 shows the *ACE2* gene polymorphisms that are possibly more vulnerable to COVID-19 and the risk of CVD. Cross-sectional human studies from Sheila et al. reported that the circulating *ACE2* gene is a genetic marker of cardiovascular disease. Paramasivam et al. [36] reported that understanding the underlying mechanism by which SARS-CoV-2 causes CVD is of greatest importance, and cardiovascular protection should be taken into consideration during treatment for COVID-19 [36]. All the above observations strongly suggested the importance of *ACE2* and its regulation in cardiovascular disease and COVID-19.

ACE2 Gene Polymorphisms as a Risk in COVID-19

The *ACE2* gene polymorphisms are linked to several diseases, which also play a main role in COVID-19 infection and its severity [24]. There are four SNPs in the *ACE2* gene, reported to be involved in modulating cardiac structure and function. One of the SNPs rs2285666 was reported to be involved in left ventricle mass in additional other three SNPs RS1978124, rs4646179. Srivastava et al. ascertained a significant positive correlation for SNP rs2285666 with COVID-19 infection susceptibility and fatality rate among the Indian population. In addition to TMPRSS2 rs2329760 SNP, *ACE2* rs2285666 SNP is one of the predictors of COVID-19 disease severity has been shown in the Egypt population. Kushal et al. [37] reported the soluble *ACE2* K26R and T92I mutants were more effective in blocking the entry of the virus suggesting that *ACE2* variants can modulate susceptibility to SARS-CoV-2 [37]. Earlier evidence reports of the C/C genotype of rs2106809 and the allele A of rs2285666 in *ACE2* are risk factors in patients with COVID19. The different SNPs of *ACE2* and rs5183 AGTR1 showed an association with severity and death in patients with COVID-19 and comorbidities [38-43]. Mayan et al. first reported a miRNA candidate that can target *ACE2* in cardiomyocytes and thus may be exploited as a therapeutic target for cardiovascular complications and COVID-19 [44]. The review finds that COVID-19 patients with severe symptoms also seem to suffer from various other health conditions including Cardiovascular

Table 1: Show the *ACE2* gene rs2285666 polymorphisms are susceptibility in Covid-19 and Cardiovascular disease.

S. Nos	COVID-19	Country	Cardiovascular Disease	County
1	Maria et al. [43]	Spain	Zhong et al. [31]	China
2	Srivastava et al. [44]	India	Lieb et al. [32]	Germany
3	Nahid et al. [45]	Iran	Huang et al. [33]	China
4	Birte et al. [46]	Germany	Ciara et al. [34]	Ireland
5	Abdelsattar et al. [47]	Egypt	Chaoxin et al. [35]	China
6	Asselta et al. [48]	Italy	Cheng et al. [36]	South African

Disease (CVD), hypertension, and diabetes [45]. Screening for the novel SNPs by focusing on recently identified SNPs in critical regions of *ACE2* can be targeted to monitor susceptibility markers for COVID-19 infection [20]. The review reports strong evidence of *ACE2* gene polymorphisms as a risk in COVID-19.

Conclusion

The *ACE2* gene rs2285666 polymorphisms, as seen in COVID-19 disease, correlated with the severity and susceptibility of COVID-19. *ACE2* gene SNP rs2285666 is also seen in CVD. Correlating, *ACE2* gene rs2285666 polymorphisms, with CVD and COVID-19 infection. We strongly believe that those who are infected with COVID-19 are more susceptible to getting CVD in near future.

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