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Angiotensin-Converting Enzyme 2 (ACE2) gene Polymorphism and susceptibility to Covid-19 infection

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ABSTRACT

(COVID-19), SARS-CoV-2 originated from Wuhan, China and has led to a worldwide pandemic. COVID-19 is a novel emerging infectious disease caused by SARS-CoV-2 characterized as atypical pneumonia. Most of the cases were epidemiologically linked to the seafood and animal market. Novel Coronavirus strains are spread from person to person through contaminated droplets from a person who is sick with the illness (through coughing or sneezing) or contaminated hands. The virus can spread through touching an infected surface. The incubation period extends from 1 to 14 days (that means the amount of time from being exposed to the virus to showing symptoms). The symptoms are: Sore throat, Fever, Shortness of breath, Cough, Headache. Most of the patients with COVID-19 have mild or moderate disease, however up to 5-10% present with severe and even life-threatening disease course. The entry of SARS-CoV-2, the agent that causes COVID-19, into the cell occurs by binding viral spike proteins to angiotensin-converting enzyme 2 (ACE2) receptors of the host membrane. It was suggested that increased susceptibility to COVID-19 infection is associated with the expression of the target ACE2 receptor in the epithelium exposed to the virus the aim of this article is to summarize the latest literature and explore how ACE2 variants influence an individual's susceptibility to SARS-CoV-2 infection.

Keywords: COVID-19. Angiotensin-converting enzyme 2 (ACE2).

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been declared as a new pandemic by the World Health Organization (WHO) on 11 March 2020. COVID-19 causes both pneumonia and acute respiratory distress syndrome (ARDS). Other COVID-19 complications may include acute liver, cardiac and kidney injury, as well as secondary infection and inflammatory response. SARS-CoV-2 is an enveloped virus containing one positive-strand RNA genome that comprises 29.9 kb. SARS-CoV-2 shares 80% identity with SARS-CoV-2, and both viruses use the angiotensin-converting enzyme 2 (ACE2) as a cellular entry receptor. SARS-CoV-2 belongs to the coronavirus β genus, structural proteins of which include S proteins, N proteins, M proteins, and E proteins[2]. It's infecting procedure shares a great similarity with SARS-CoV-2, by binding to the angiotensin-converting enzyme 2 receptor on the outside membrane, the virus gradually fuses into the host cell, causing great damage to its original function. This novel coronavirus is mainly transmitted by aerosol like respiratory droplets generated during coughing and sneezing by symptomatic patients[1, 2, 3].

Coronavirus (SARS-Cov-2) can infect and damage the lung cells. This hyper-inflammatory state is due to a cytokine storm resulting in organ failure (e.g., lung, heart, and kidney). It has been shown that imbalance in renin-angiotensin system (RAS) is the main pathophysiological reason of ARDS. In details, RAS made up of two main arms: the inflammatory axis which consists of angiotensin converting enzyme (ACE)/Angiotensin II (Ang II)/angiotensin type-1 receptor (AT1R), and the anti-inflammatory axis which includes angiotensin-converting enzyme 2 (ACE2)/Ang-(1–7)/Mas Receptor (MasR). ACE2 is a counter-regulatory enzyme that converts angiotensin-2 to Ang-(1–7) form in the renin-angiotensin system. Considering the impact of ACE2 on both arms of RAS and the opposite function of each arm, ACE2 shows a dual role in Covid-related ARDS. On the one hand, ACE2/Ang (1–7) system protects the lung against ARDS by its anti-inflammatory/anti-oxidant function through converting Ang II. On the other hand, SARS-Cov-2 can use ACE2 for host cell entry. This entrance causes antiserum rise against ACE2 blocking the further virus infection [4, 5, 6]

Zou et al. linked the ACE2 expression in different organs to their potential risk to SARS-CoV-2 infection. High-risk tissues were defined as containing cells types with > 1% proportion of ACE2 expression and were included in this category: lower respiratory tract (2%), lung (> 1%), heart (> 7.5%), ileum (30%), esophagus (> 1%), kidney (4%), and bladder (2.4%). To note, stomach and liver samples had < 1% proportion of ACE2-positive cells, indicating that these tissues were considered as low risk for SARS-CoV-2 infection. Of importance, ACE2 expression in nasal epithelium occurs in an age-dependent manner and

may explain, at least in part, the reason why the younger ones have lower incidence of COVID-19, since they exhibited the lowest nasal gene expression of ACE2. Additionally, the lower expression of ACE2, not only in nasal epithelium but also in bronchial epithelial cells in children, when compared to adults, may also explain the non-respiratory COVID-19 symptoms/clinical manifestations in the youngest[7].

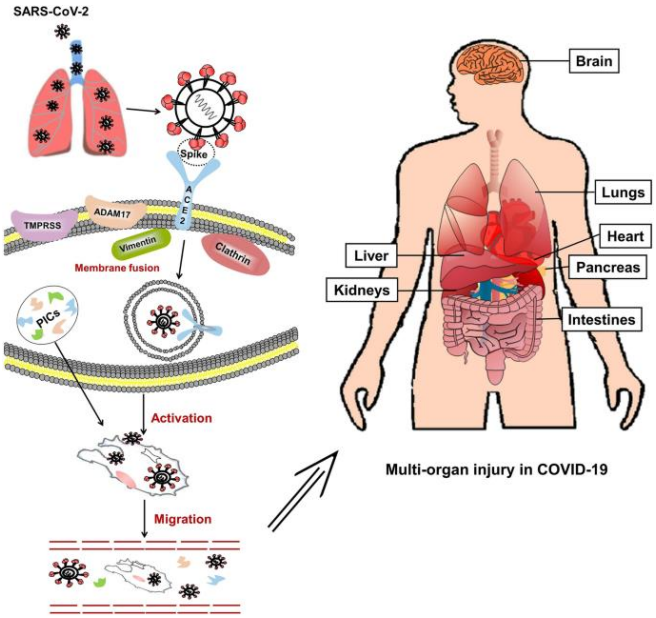

Figure 1: **SARS-CoV-2 life cycle: from binding to ACE2 receptor to shedding**

ACE2 is mainly expressed in the intestines, kidneys, myocardium, vasculature and pancreas, while lower expression occurs in the respiratory system. Varied symptoms and outcomes of COVID-19 might be associated with the pattern and level of human ACE2 enzyme expression in different tissues [8]. Unlike the attached type, free circulating form of ACE2 might prevent SARS-Cov-2 entry to pulmonary endothelium. Thus, the severity of COVID-19 infection can be correlated to the proportion of attached/soluble ACE2 [9]. The gene for ACE2, present on chromosome X (Xp22) comprises of 39.98 kb of genomic DNA and has 18 exons [10]. Many ACE2 variants are associated with several common diseases, whose incidence depends on the balance in the renin-angiotensin-aldosterone (RAAS) pathway. Hypertension is associated with rs1514283, rs2074192, rs233575, rs4646155, rs4646176, rs2285666, rs879922, rs2106809, rs4646188, rs4240157, rs4830542, rs2158083, and rs879922 [11]. The role of ACE2 is very critical since the inhibition of RAAS pathway leads to upregulation of ACE2 which alleviates ARDS and myocarditis symptoms in COVID-19 patients but at the same time increased ACE2 expression may increase the entry of virus into host cells,

complication the overall clinical picture [12].

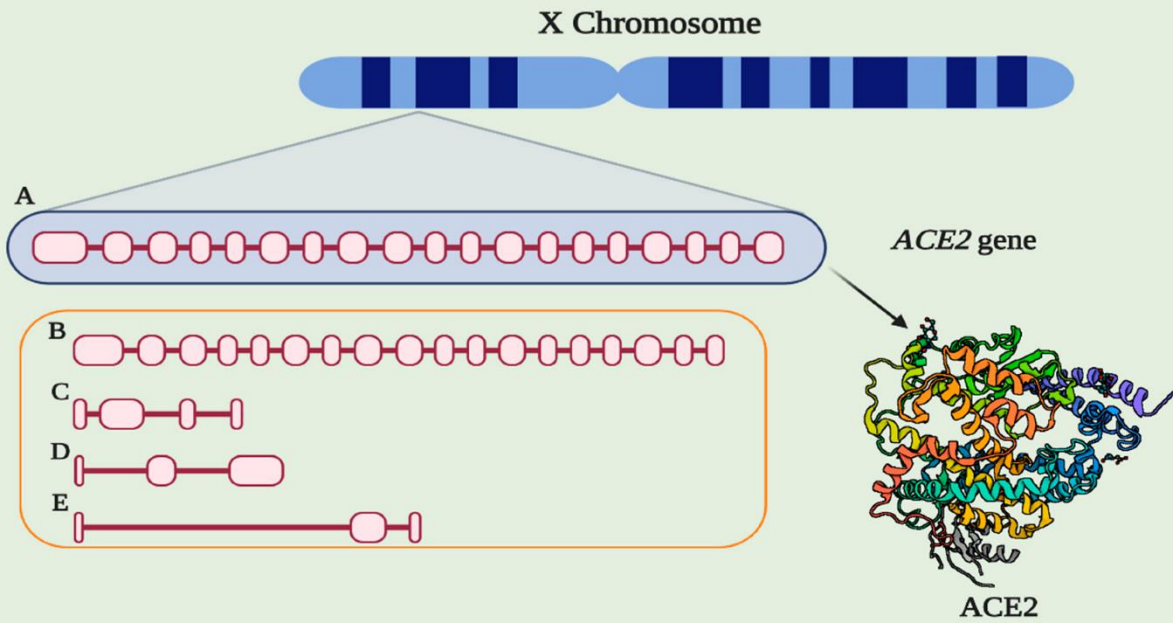

Figure 2: ACE-II gene Polymorphism

Recent studies identified ACE2 polymorphisms that might influence disease severity and indicated that out of 10 studied SNPs, 5 polymorphisms (rs6632680, rs4830965, rs1476524, rs4240157 and rs2048683) indicated an association with higher tissue specific expression of ACE2 resulting in hospitalization whereas rs1548474 polymorphism showed correlation with low tissue expression and lesser severity [13, 14].

Variation in circulating ACE2 levels was speculated to be controlled by genetic factors including rs2106809 polymorphism [13]. Xiao et al., [15] have earlier reported that a point mutation in the ACE2 gene (Leu584Ala) facilitates entry of SARS-CoV-1 into host cells. Recent studies have proven that several amino acid variants can potentially affect the interaction between the viral S1 protein and ACE2 receptors and thus the level of infection [16]. Different amino acid residues expressed within the ACE2 receptor were observed to be very relevant either by promoting or preventing viral infection. Wooster et al., [17] reported that ACE2 rs4240157 polymorphisms is associated with COVID-19 disease severity as it might be inducing higher tissue specific expression of ACE2 resulting in the hospitalization of COVID-19 patients. Pouladi et al., [18] reported the association ACE2 rs4240157 T > C gene polymorphism with hypertension and other related heart diseases.

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