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COVID-19 and the Angiotensin-Converting Enzyme 1 D/I Genotype: Protection of People at High-Risk by Predicting the Severity of the Disease

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About the Study

Throughout history, humans have been threatened by various infectious diseases [1]. As of August 22, 2020, a new coronavirus infection, COVID-19, has been raging around the world, infecting approximately 23 million people and killing approximately 800,000 [2,3]. Although COVID-19 is a serious infectious disease, it is at most comparable to the 1968 Hong Kong flu given the far more deaths caused by previous devastations, such as the plague, smallpox, Spanish flu, AIDS, tuberculosis and malaria [1]. However, we are still in the midst of the epidemic, and it is difficult to project the extent of damage COVID-19 will ultimately inflict.

A major characteristic of COVID-19 is that the infectivity and pathogenicity of the causative SARS-CoV-2 virus are strongly specific to 'an area or ethnic group' [4,5]. About two-thirds of the world's dead are in Western countries, including Latin America [2,3]. To the best of our knowledge, a similar pattern has never been recorded for any of the above pandemics. Historically, most outbreaks have originated in Asia and then spread to Europe without showing noticeable differences in mortality effects on different peoples. The most recent examples are other corona infections, the 2002 SARS and 2012 MERS, the former of which gave rise to the level of pandemic [6,7]. SARS caused about 770 deaths (mean mortality rate, 9.4%) and MERS about 520 deaths (mean mortality rate, 34%). Ethnic differences played no role in patient mortality in either disease. The unique ability to recognise ethnic differences by COVID-19 has attracted the attention of researchers, many of whom view this as a case of genetic predisposition to this infection by the host. Many attempts worldwide have been made to identify the genes involved, and very recently, we found that angiotensin-converting enzyme (ACE) 1, a prototype ACE molecule, is strongly correlated with SARS-CoV-2 infectivity or pathogenicity [5]. ACE1 is a key molecule of the renin-angiotensin-aldosterone system (RAAS) [8-10], while ACE2 is a receptor for SARS-CoV-2 [11-13]. The RAAS is essential in regulating blood pressure, electrolyte balance and extracellular volume. There are several candidate genes that may be involved in genetic predisposition; however, mechanistically, we consider the ACE1 D/I genotype to be the most likely candidate. The reasons are provided below.

The human ACE1 gene on chromosome 17 has an insertion (I) or deletion (D) of the Alu repeat sequence in intron 16 [14]. Therefore, there are three different genotypes in the I/D polymorphism: II, ID, and DD. Since an exodus of our ancestors from Africa about 100,000-200,000 years ago, European and Asian people have continued to travel east and west across the vast Eurasian continent, during which time our ancestors have undergone genetic changes. We found that the ACE1 II genotype frequency in a population was negatively correlated with the number of SARS-CoV-2 cases and the number of deaths due to SARS-CoV-2 infection [5]. Human geographical eastward migration appears to be consistent with a gradual increase in the frequency of the ACE1 II genotype. The Mantel test results shows that there is a significant correlation between geographical distance and genetic distance between populations [15]. Therefore, it is worth noting that the frequency of ACE1 II genotype is inversely related to susceptibility to virus infection and mortality.

COVID-19 is a systemic infection closely associated with various symptoms and comorbidities, such as hypertension, type 2 diabetes, chronic renal failure and ischaemic heart disease. The effects of viral infection extend to most major organs and systems, likely due to the rather ubiquitous expression and distribution of the viral receptor, ACE2. ACE2 is broadly expressed in the vascular endothelium of the lung, which is the principal target of SARS-CoV-2 and the main site of injury, and in the heart, kidneys and digestive tract [11-13]. RAAS is composed of two axes: the ACE1-AngII-AT1 receptor axis and the ACE2-Angiotensin1-7-Mas receptor axis. Together with aldosterone, RAAS is deeply involved in maintaining homeostasis in the body. The AngII peptide of the ACE1-AngII-AT1 receptor axis is involved in the positive activation of vasoconstriction, aldosterone secretion, Na+ and water retention, fibrosis, enhanced inflammation and thrombosis. Meanwhile, the Ang-(1-7) peptide functions as a protector via the Mas receptor by suppressing the effects of AngII peptide. Therefore, excess AngII results in an imbalance between the two axes, producing deleterious effects that can be especially remarkable. In addition, SARS-CoV-2 infection induces the downregulation of ACE2 following viral adsorption, similar to SARS-CoV-1 infection [16-19]. In individuals with underlying health problems or comorbidities, this downregulation of ACE2 is believed to further promote higher levels of ACE2 deficiency and Ang II expression through reducing its degradation sufficient to create clinical ramification [9,19]. Furthermore, diabetes may be associated with reduced ACE2 expression [20,21], probably as a result of the glycosylation. The same process may also happen to high-risk people, such as the elderly. ACE2 expression in the lungs markedly decreases with ageing [22], a phenomenon that occurs to a greater extent in men than in women.

International research teams in the United Kingdom and other countries have estimated that the population most at risk of suffering from severe effects when infected by the new coronavirus comprises 22.4% of the world population, or about 1.7 billion people [23]. This population is 30.9% European, 28.3% North American, 22.5% Asian and 16.3% African. This estimate agrees well with the reality that Western societies have suffered the most deaths from COVID-19. One interpretation of the current situation is as follows: in Western developed countries that have achieved long life expectancies, the proportion of high-risk people, such as those with comorbidities, is high; thus, the number of infected people and deaths is also high.

However, a closer analysis of the data reveals that this not to be the case. For example, the five major countries in Central Europe, namely, Italy, Spain, France, the United Kingdom and Germany, have over 100 times more deaths (number of deaths/million) than the East Asian countries of China, South Korea, Japan and Taiwan [2,3,5]; however, the average levels of high-risk people in both regions are almost the same, that is, about 30% of their respective populations. Looking at specific countries, the proportion of high-risk people in Japan, whose life expectancy is the oldest in the world, is 33.4%, well above the world average, but the country's death toll is extremely low at 9 out of 1 million [2,3]. In Taiwan, where the high-risk population is even higher than in Japan, the death toll is only 0.3 out of 1 million [2,3]. It is more likely that the difference in fatalities between Central Europe and East Asia is more related to differences in the ACE1 genotype than in living standards. If so, then the ACE 1D allele may play an active role in coronavirus infections.

Since ACE2 is a viral receptor, it has been the focus of most current research. However, our study suggests for the first time that the ACE1 genotype may be strongly involved in the pathogenesis of COVID-19. As described above, the equilibrium of RAAS is maintained by the positive and negative actions of the ACE1-AngII-AT1 and the ACE2-Angiotensin1-7-Mas receptor axis, respectively. Therefore, ACE2 acts as a suppressor in RAAS. However, it is also important to view the role of ACE1 and AngII as accelerators when considering the reason for the imbalance of the system. The ACE 1 D allele is known to be associated with many comorbid conditions, such as hypertension [24], type 2 diabetes [25], acute respiratory distress syndrome (ARDS) [26,27], venous thromboembolism and myocardial infarction [28]. This suggests that people suffering from these comorbidities may have a high proportion of the ACE 1 D allele. This is a hypothesis that should be carefully studied as soon as possible. For this, please also refer interesting reviews written by Morris [29] and Gard [30]. More importantly, a marked difference in serum ACE levels has been observed between subjects in each of the three ACE genotype classes. Rigat et al. reported that serum immunoreactive ACE concentrations were 299.3, 392.6 and 494.1 micrograms/litre, for homozygotes with the II, DI and DD alleles, respectively [31]. Biller et al. also reported that serum ACE levels and ACE genotypes correlated significantly, with the highest serum ACE levels found in subjects with the DD ACE genotype, while the lowest serum ACE levels were found in subjects with the II genotype [32]. According to Ruprecht et al. the mean serum ACE levels in individuals with the genotypes DD, DI and II are 59.8, 47.7 and 32.2 Unit/liter, respectively [33]. Actually, Úri et al. reported that circulating ACE2 would be an appropriate biomarker of systolic dysfunction in human hypertension and heart failure [34]. The risk of acute myocardial infarction increased significantly when the serum levels of AngII and KLK1 simultaneously increased [35]. The amount of ACE in serum seems to be proportional to its catalytic activity [29]. These data indicate that the physiological level of ACE1 expression in the D carrier is significantly higher than that in the II carrier, suggesting that the standard ACE1-AngII-AT1R axis level is also high in the D carrier. This effect may not be important under normal conditions, but when a person is infected with the new coronavirus, then the infection may exert an enormous exacerbating effect. The effect is expected to be especially severe among DD carriers, where coronavirus infection may cause an imbalance that leads to the development of full-blown COVID-19. However the D/I genotype differences may not be straightforward, as seen in the confusing situation of the Middle East, where there should be more D allele carriers than in Europe [5,15]. In the Middle East, the number of people infected by the new coronavirus is as high as that in Europe, but the mortality rate is between the levels of Europe and Asia, i.e. not as high as in Europe [2,3]. It remains unclear whether this difference can be explained by the delayed onset of the coronavirus epidemic in the Middle East compared to Europe or whether there are other reasons such as involvement of genotypes adding to risk conferred by D allele. At this point, what is clear is that these issues will require further diligent verification.

We predict that there will soon be an urgent need worldwide to investigate the relationship between the D allele and the severity of COVID-19. If our predictions are correct, then higher numbers of COVID-19 patients and more severely ill patients will be found in groups with the DD genotype and the D allele and this marker will be lower in the asymptomatic and healthy groups. However, it may not be easy to show such differences statistically. This is because the difference between the ACE1 genotypes in the West and the East is not so large (typically, the frequencies of DD, DI, II are roughly 30, 50 and 20% [36], and 10, 50 and 40% [35], in the United Kingdom and China, respectively). Therefore, a substantial number of samples may need to be tested to prove this hypothesis. Comorbidities aggravated by the SARS-CoV-2 infection cover almost all systemic diseases, which affect the cardiovascular, urological and immune systems. As the need increases, it will be necessary to automate the ACE1 genotyping test. Such a diagnostic system may be able to predict the severity of the disease in those who are at high-risk (patients with comorbidities, elderly men, HIV-infected persons, the obese and smokers). Currently, there are new corona vaccines being developed worldwide. Establishing a convenient test system will be important for determining the priority of vaccine administration. Elderly people in care homes in developed European countries, especially Sweden, the United Kingdom and Belgium, account for about 30%-50% of each country's deaths [37]. Saving the lives of these people is an important task that should be prioritised over other COVID-19 issues. As in Japan and the Scandinavian countries of the past, the world is now aging rapidly. It is critical to know how to protect such people by maintaining their comorbidity-free state. The fact is that we know very little about the association between the ACE genotypes and the patients with the comorbidities prevalent in elderly facilities. The reason for this is the tests needed are special and not generally performed. For example, it will be very important to know the exact RAAS situation of people in elderly facilities. This means that comprehensive measurements of actual levels of RAAS components such as renin, AngII, ACE1, ACE2 and Ang-(1-7) in the serum are essential. In addition, the active roles of free and cell-associated ACE1 and ACE2 should be extensively examined. Similarly, it will be important to determine the role of cell surface proteases, such as ADAM17 (which cleaves cellular ACE2) [38] and TMPRSS2 [11]. The concomitant determination of a person's ACE genotype along with actual measurements of RAAS components in the serum will help to improve the situation of people vulnerable to this disease. Infectious diseases are by nature inherently discriminatory, i.e. they do not infect everybody equally. This pandemic has shown us that the spread of the coronavirus infection varies by race, age, sex and poverty status.

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