ScieniQ Publishers

Journal of Cardiology & Cardiovascular Research

Research Article

Coronavirus disease 2019 and the renin-angiotensin system: the role of angiotensin-converting enzymes 1 and 2, and the effect of gene polymorphism

Shoji Haruta, MD

Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center, Chiba, Japan

***Corresponding author**
Shoji Haruta, MD, Department of Cardiology, Tokyo Women's Medical University, Yachiyo Medical Center, 477-96, Oowada-shinden, Yachiyo, Chiba, 276-8524, Japan

Received : 13 Nov 2020
Accepted : 16 Nov 2020
Published: 20 Nov 2020

Abstract

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic; however, there have been differences in the number of patients and deaths per country, with fewer cases in East Asia than in Europe and the United States. The binding of SARS-CoV-2 to angiotensin converting enzyme (ACE) 2 on the cell surface of the host decreases ACE2 expression, increases angiotensin II, and influences the renin-angiotensin system (RAS). ACE polymorphism varies according to race, and differences in expression levels of ACE and ACE2 exist. Race-based differences in the gene encoding the protein, including ACE associated with SARS-CoV-2, may affect the prevalence and severity of COVID-19. Recently, some studies have been conducted on the relationship between ACE polymorphism and COVID-19, but there is no consensus. Here, the changes of RAS in COVID-19, the relationship between gene polymorphisms associated with SARS-CoV-2 infection and race, differences in the effect of gene polymorphisms on RAS during infection, and the significance of angiotensin-based inhibitors have been described.

Key words: COVID-19, renin-angiotensin system, gene polymorphism

Introduction

Coronavirus disease (COVID-19), the spread of which was reported in China in early January 2020, has reportedly led to infections in >40 million people and 1.1 million deaths worldwide. This information was confirmed as per findings reported by Johns Hopkins University as of October 21, 2020 [1]. The COVID-19-related death toll per million people has remained high in Western countries, including the United States (24,994 people), Brazil (24,811 people), Argentina (22,546 people), France (14,259 people), South Africa (11,908 people), and the United Kingdom (11,232 people). Meanwhile, deaths reported have been extremely low in East Asian countries, including Taiwan (23 people), Thailand (53 people), South Korea (456 people), and Japan (743 people) (Fig. 1) [2]. Western countries reporting a high death toll despite strict measures such as city lockdowns, show paradoxical data as East Asian countries like Japan, which only conducted gradual restrictions on movement, reported low death tolls. Differences in the virus type, blood type, genetics (e.g., race, sex), epigenetics (e.g., acquired immunity), public health policies (e.g., BCG vaccination), government measures (e.g., outdoor activity restrictions), and public health awareness campaigns (e.g., mask-wearing) are thought to be reasons for regional differences; however, the role of all the above-mentioned factors remains unclear.

COVID-19 invades and infects cells via membrane protein activity of ACE2 [3]. Gene polymorphisms of ACE and ACE2 have been reported to vary by race [4], and the presence or absence of associations with prevalence and mortality of COVID-19 has been noteworthy.

Recently, some studies have been conducted on the relationship between ACE polymorphism and COVID-19, but there is no consensus [5,6]. In this review, changes in the renin-angiotensin system (RAS) in COVID-19 patients, the relationship between gene polymorphisms associated with SARS-CoV-2 infection and race, differences in the effect of gene polymorphisms on RAS during infection, and the significance of angiotensin-based inhibitors have been discussed.

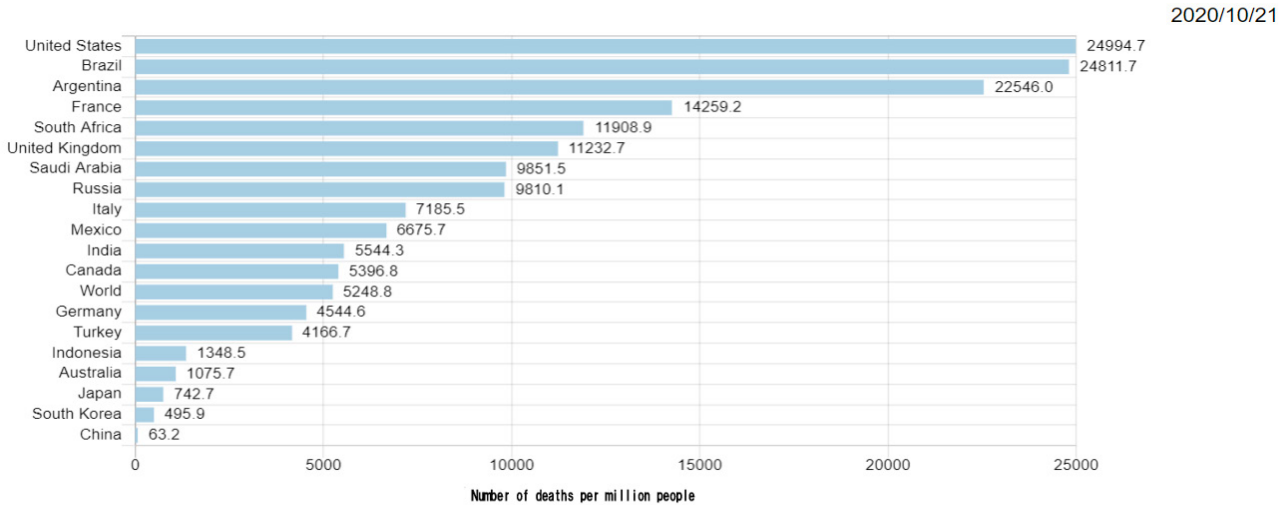

Figure 1: Number of deaths due to COVID-19 per million people in each country worldwide

The COVID-19-related death toll per million people has remained high in Western countries, including the United States, Brazil, Argentina, France, South Africa, and the United Kingdom. Meanwhile, deaths reported have been extremely low in East Asian countries, including Taiwan, Thailand, South Korea, and Japan.

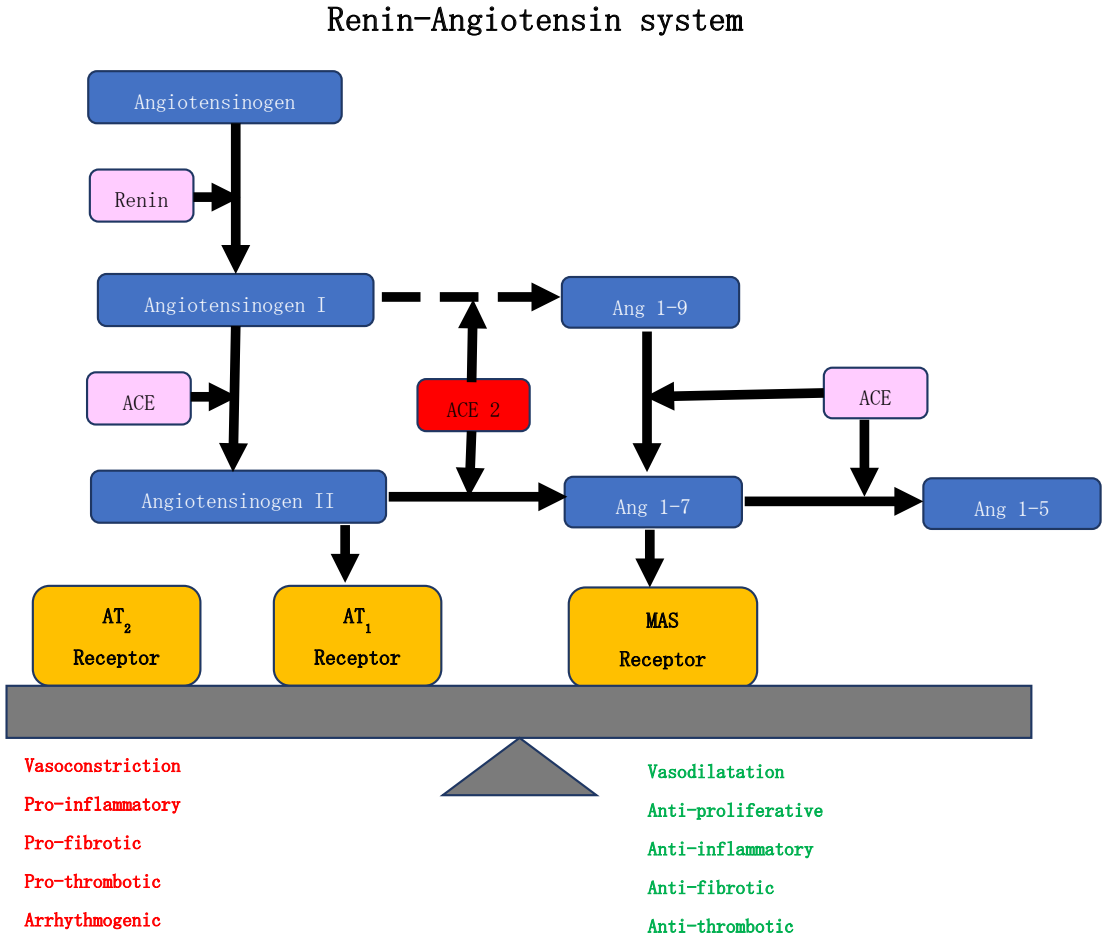

Figure 2: Angiotensin-converting enzyme (ACE) converts angiotensin-(1–7) (Ang 1–7) to angiotensin-(1–5) (Ang 1–5). The inhibition of ACE can lead to elevated levels of Ang 1–7, resulting in vasodilation and the like (green type). ACE2 converts angiotensin I and II to angiotensin 1-9 and Ang 1-7, respectively. The inhibition of ACE2 can lead to elevated levels of Angiotensinogen II, resulting in vasoconstriction and the like (red type). AT1; angiotensin II type 1 receptor. AT2; angiotensin II type 2 receptor.

ACE and RAS

Angiotensin converting enzyme (ACE) is a metalloprotease that encodes 805 amino acids, located on the X chromosome (Xp22.2), and is a single-cell-catalyzed type I transmembrane glycoprotein containing a protein domain [7,8]. ACE plays an important regulatory role in RAS, converting inactive angiotensin I (Ang I) to angiotensin II (Ang II), which regulates vasoconstriction. Ang II is the core of RAS and catalyzes various biological reactions through the angiotensin type 1 receptor (AT1R) and type 2 receptor (AT2R). ACE2 is a homolog of ACE, producing angiotensin (1-9) from Ang I and angiotensin (1-7) from Ang II. Ang II binds to AT1R on the muscle cell surface of microvessels, thereby causing vasoconstriction. It also promotes the reabsorption of salt in kidneys. Both vasoconstriction and salt reabsorption contribute to elevated blood pressure. Ang 1-7 induces vasodilation through its action on the Mas receptor (MasR), lowers blood pressure, and has opposite effects on Ang II such as anti-inflammation [9]. Ang 1-7 counteracts and antagonizes Ang II functions (e.g., vascular relaxation, vascular permeability suppression, anti-inflammatory actions) and exhibits organ-protective effects [10]. ACE and ACE2 are important enzymes that regulate the balance between Ang II and Ang 1-7, and ACE2 is directly affected by SARS-CoV-2. ACE2 expressed in the lungs (mainly alveolar type II cells) is the main invasion source of SARS-CoV-2 [11]; however, ACE2 is also highly expressed in the heart and blood vessels. Therefore, this study aimed to counteract the effects of Ang II in conditions with excessive RAS activation, such as hypertension, congestive heart failure, and atherosclerosis.

SARS-CoV-2 and RAS

SARS-CoV-2 binds to ACE2 on the membrane surface of target cells via the spike protein on the virus surface. Part of the spike protein is cleaved through the actions of transmembrane serine protease 2 (TMPRSS2) and cathepsin B/L, and cell invasion occurs as a result of fusion between the virus envelope and the cell membrane [12]. It has been reported that intracellular infection of the virus suppresses ACE2 infection, and increases angiotensin II (Ang II) may induce lung damage [13].

Ang II activates angiotensin type 1 receptor (AT1R) and a disintegrin and metalloprotease 17 (ADAM17), which is a protease present on the cell membrane. ADAM17 cleaves ACE2 from the cell surface to produce soluble ACE2 [14].

Soluble ACE2 binds to the spike proteins of SARS-CoV-2 and likely suppresses viruses binding to ACE2 on the cell membrane [15]. However, blood levels of soluble ACE2 generated in vivo are markedly low, and a small percentage of AC2 present in the cell membrane; therefore, clinical trials using recombinant soluble ACE2 formulations are currently being conducted. ADAM17, activated by AT1R stimulation, also cleaves the precursor tumor necrosis factor α (TNFα) and interleukin-6 receptor α (IL-6Rα), thereby releasing TNFα and soluble IL-6Rα. TNFα activates nuclear factor-κB (NF-κB) via the receptor and induces the production of various inflammatory cytokines, including IL-6 which causes a cytokine storm. Therefore, angiotensin II receptor blockers (ARBs) and anti-IL-6 antibodies have been hypothesized to suppress cytokine storms [16].

Comparison between race and genes associated with SARS-CoV-2 infection

Lee et al. investigated whether region- or ethnic group-based differences existed in the genes that encode the seven proteins (ACE2, TMPRSS2, cathepsin B/L, toll-like receptor (TLR) 3/7/8) associated with SARS-CoV-2 infection, and published results of comparative investigations on differences in the initial mechanism of virus infection [5]. Cleavage facilitated by TMPRSS2 and cathepsin B/L is required for binding of SARS-CoV-2 with the cell surface and for cell invasion. Thereafter, virus RNA binds to proteins (receptors) TLR3/TLR7/TLR8 within the cell. Binding to these receptors triggers an innate immune response. Three comprehensive human gene diversity databases (gnomAD, Korean Reference Genome Database, TogoVar) and three whole-genome sequence databases (The 1000 Genomes Projects, Gene-Tissue Expression, Simons Genome Diversity Project) were extensively searched for gene sequences encoding the seven proteins involved in SARS-CoV-2 infections, and a comparative investigation was conducted based on regions and ethnic groups [17-19]. The presence of any functional differences in these seven proteins was also investigated using data on gene sequence and protein structure/function. Of the full-length amino acid sequence of the ACE2 protein, there were 33 amino acids which were found to be directly involved in binding SARS-CoV-2. However, 19 gene variants were found in gene sequences encoding these 33 amino acids, with an average occurrence of 0.03%. Of these, the variant sequence K26R was the most common (0.39%), and region- and ethnic group-based differences were present. East Asian populations had the lowest frequency of this sequence (0.007%), and non-Finnish European populations had the highest frequency (0.59%). However, this amino acid substitution mutation was not expected to affect the ACE2 protein function based on its molecular structure. Furthermore, the variant sequence K31K had the highest frequency in East Asian populations (0.022%), with the Japanese population having a predominantly high frequency (0.23%, analyzed genome number = 3552), when compared with the Korean population (0.029%, analyzed genome number = 1722). This variant does not affect the amino acid sequence; therefore, there is no alteration in ACE2 protein function. All other gene variants had low frequencies (<0.1%) and did not change the function of ACE2 with regard to molecular structure, irrespective of the presence or absence of changes in amino acid substitution. Similarly, the results for TMPRSS2 and cathepsin B/L enzyme activity, and binding ability of TLR3/TLR7/TLR8 on viral genome RNA demonstrated the presence of mutations that caused dysfunction observed in the genes encoding each protein; however, their frequencies were 0.01%, and no region- or ethnic group-based differences were observed. Furthermore, the number of loss-of-function mutations calculated and predicted from the size of the ACE2 and TLR7 genes were 31 and 20.7, respectively; however, actual data analysis conducted in this study showed only 3 and 2, respectively. This was attributed to evolutionary pressure (selective pressure) that maintained the functions of these two molecules during human evolution. Thus, it was reported that no region- or ethnic group-based differences were present in the initial binding between SARS-CoV-2 and human cells, and the gene sequence of the molecular group was involved in the initial innate immune response.

The ACE (ACE1) gene is located on the long arm of chromosome 17 (17 q 23), and contains 26 exons (sections translated from DNA to protein) and 25 introns (sections not translated to the protein). There are insertion alleles (I: insertion) and deletion alleles (D: deletion) depending on the presence or absence, respectively, of 287 base-pair Alu repeat sequences of ACE1 intron 16, and this can be classified into three genotypes (type II, type ID, and type DD) [20,21].

Yamamoto et al. reported on the relationship between the ACE genotype and SARS-CoV-2 infection [6]. Results showed that the frequency of the ACE1 II (insertion/insertion) genotype in a given group was significantly and negatively correlated with the number of patients infected with SARS-CoV-2. Similarly, ACE1 II genotypes negatively correlated with the number of deaths due to SARS-CoV-2 infection. These data suggest that ACE1 II genotypes may affect the prevalence and clinical outcome of COVID-19 and function as a biomarker for prediction of COVID-19 risk or severity. The correlation between either insertion or deletion genotypes (I/D [insertion/deletion] genotypes) in ACE1 genes of Europeans and Asians, and the prevalence and mortality rate of SARS-CoV-2 were investigated.

Results showed that both the number of patients infected by SARS-CoV-2 and those who died from COVID-19 significantly and negatively correlated with the frequency of ACE1 II genotypes (R = -0.847 and -0.755, respectively). The European population had a lower ACE1 II genotype frequency and a higher prevalence and COVID-19-related mortality compared to that in the Asian population. This study also investigated single nucleotide polymorphisms (SNPs) contributing to SARS-CoV-2 pathogenicity, such as ACE2, CTSL (cathepsin L), and TMPRSS 2; however, no significant correlations were observed with the prevalence or mortality rate of COVID-19. These results suggest that ACE1 I/D polymorphisms may serve as a genetic biomarker for the infectivity and pathogenicity of SARS-CoV-2. Notably, increases in the frequency of ACE1 II genotypes were inversely correlated to SARS-CoV-2 infections and mortality rate. The mortality rate, proportional to the number of infected and afflicted patients, and is also independently or additionally affected by infection/affliction conditions. These results are the first indication that the prevalence of the D allele in ACE1 may be involved in the susceptibility to SARS-CoV-2 infection and the exacerbation of COVID-19 symptoms such as pneumonia.

Under physiological conditions, the signal from Ang II produced by ACE1 is associated with pathological conditions such as vasoconstriction, inflammation, and fibrosis, and the ACE2-derived peptide Ang 1-7 reverses Ang II activity via the Mas receptor. Therefore, the balance between ACE1 and ACE2 is considered vital for maintaining homeostasis in the body.

It has been reported that individuals with DD genotypes demonstrate significantly higher serum ACE1 levels than individuals with either an ID or II genotype [22]. Furthermore, ACE2 expression was suppressed by SARS-CoV-2 infection and might induce ACE1/ACE2 imbalances that contribute to overactivation of the renin, angiotensin, aldosterone system, and cardiopulmonary function suppression. This further reduces the effect of ACE2, which counteracts the pathophysiological effects of Ang II produced by ACE1, potentially exacerbating the pathological condition.

Patients with the D allele, particularly those with the DD genotype, have been reported to demonstrate a higher prevalence and mortality rate of acute respiratory distress syndrome (ARDS) and certain cardiac, pulmonary, and inflammatory diseases [23,24]. It is predicted that COVID-19 patients with ACE1/ACE2 imbalances, in other words, patients with D alleles or DD genotypes, particularly for ACE1, tend to experience more severe conditions.

ACE1 I/D polymorphisms are also associated with the coughing reflex [25]. Aspiration due to a decrease in age-related coughing is the primary cause of pneumonia among the elderly [25]. ACE1 D alleles have previously been reported to contribute to pneumonia risk among the elderly in Japan [27]. High ACE1 expression in ACE1 DD genotypes decreases substance P and increases the risk of pneumonia by reducing the coughing reflex [28]. A Chinese meta-analysis of 12 studies related to pneumonia and ACE1, including studies from Japan and the Netherlands, reported that ACE1 I/D polymorphisms and pneumonia risk were significantly correlated [28].

A unique circumstance with high infection rates and low mortality rates has been reported in the Middle East. The relationship between SARS-CoV-2 and genetic factors in the Middle East will be an important focus for future studies. Data accumulation from various countries, including the United States, is expected to provide a more accurate understanding of the role played by ACE1 I/D polymorphisms in SARS-CoV-2 infection and COVID-19-associated prevalence and mortality rates.

RAS-based inhibitors and COVID-19

Studies suggesting the possibility of RAS inhibitors increasing the risk of development or aggravation of COVID-19 have been published [29,30]. The basis for the studies included data obtained from preliminary research which showed that RAS inhibitors increased ACE2 expression [31,32]. In the disease models used by the above-mentioned studies, reduced ACE2 expression was restored or maintained to levels that were comparable to those of the normal control group by RAS inhibitors; however, observations reported only included ACE2 expression levels that were twice the normal levels. Furthermore, the RAS inhibitor dose used in each study was much higher than the clinical doses, and it is difficult to ascertain if this exerted a clinical effect. Previous research has not reported any RAS inhibitor-mediated increase in ACE2 expression levels that could affect COVID-19 infectivity.

Meanwhile, studies on lung injury models have shown that ACE2 suppresses lung inflammation by suppressing Ang II and inflammation with ACE inhibitors and angiotensin receptor blockers [31].

ACE inhibitors/ARBs have also demonstrated potential benefits to patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) [32,33]. ACE inhibitors/ARBs can exert anti-inflammatory and antioxidant effects through upregulation of ACE2 and may be beneficial in prevention of ALI and ARDS. These drugs may play an important role in the treatment of patients with severe COVID-19, based on the pathophysiology of SARS-CoV-2 infection and the multi-faceted effects of ACE inhibitors/ARBs.

Limitations

There are few studies on the relationship between ACE polymorphism and COVID-19, and further researches are needed to reach consensus.

Conclusions

The infection and mortality rates of COVID-19 are low in East Asia compared to those in the West. SARS-CoV-2 infection occurs via ACE2; however, where race-based differences exist, ACE gene polymorphisms may potentially be a reason for these regional differences. In these instances, the ACE1 and 2 balance may be associated with infection and aggravation, and ACE inhibitors and ARBs may potentially affect pathological conditions, thereby becoming a treatment option.

Conflicts and interest

The author declares no conflict of interest.

Acknowledgments

This review did not receive any specific grant from funding agencies in the public, commercial, or not- for-profit sectors.

References

1. Coronavirus - World Health Organization 2020.1021 https://covid19.who.int/
2. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University. 2020.1021 https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6
3. Turner AJ, Hiscox JA, Hooper NM (2004) ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci. 25:291-4, Nat Rev Cardiol. 2020 Mar 5. doi: 10.1038/s41569-020-0360-5.
4. Barley J, Blackwood A, Carter ND, Crews DE, Cruickshank JK, Jeffery S, Ogunlesi AO, Sagnella GA. Angiotensin (1994) converting enzyme insertion/deletion polymorphism: association with ethnic origin. J Hypertens. 12: 955-7.
5. Lee IH, Lee JW, Kong SW (2020)A survey of genetic variants in SARS-CoV-2 interacting domains of ACE2, TMPRSS2 and TLR3/7/8 across populations. Infect Genet Evol. 85: 104507.

6. Yamamoto N, Ariumi Y, Nishida N, Yamamoto R, Bauer G, Gojobori T, Shimotohno K, Mizokami M. (2020) SARS-CoV-2 infections and COVID-19 mortalities strongly correlate with ACE1 I/D genotype. Gene. 758: 144944
7. Tipnis SR , Hooper NM, Hyde R, Karran E, Christie G, Turner AJ (2000)A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril-insensitive carboxypeptidase. J Biol Chem. 275: 33238-43.
8. Vickers C, Hales P, Kaushik V, Dick L, Gavin J, Tang J, Godbout K, Parsons T, Baronas E, Hsieh F, Acton S, Patane M, Nichols A, Tummino P (2002) Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem. 277: 14838-43.
9. Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, Acton S (2000) A novel angiotensin-converting enzyme–related carboxypeptidase (ACE2) converts angiotensin I to angiotensin. Circ Res. 87: e1-9.
10. Iwai M, Horiuchi M. Devil and angel (2009) in the renin-angiotensin system: ACE-angiotensin II-AT1 receptor axis vs. ACE2-angiotensin-(1-7)-Mas receptor axis. Hypertens Res. 32: 533-6.
11. Zhao Y, Zhao Z, Wang Y, Zhou Y, Ma Y, Zuo W (2020) Single-cell RNA expression profiling of ACE2, the receptor of SARS-CoV-2. Am J Respir Crit Care Med. 202: 756-9.
12. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D (2020) Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell. 181: 281-92. e6.
13. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 11: 875-9.
14. Lambert DW, Yarski M, Warner FJ, Thornhill P, Parkin ED, Smith AI, Hooper NM , Turner AJ. Tumor (2005) necrosis factor-α convertase (ADAM17) mediates regulated ectodomain shedding of the severe-acute respiratory syndrome-coronavirus (SARS-CoV) receptor, angiotensin-converting enzyme-2 (ACE2). J Biol Chem. 280: 30113-9.
15. Chan KK, Dorosky D, Sharma P, Abbasi SA, Dye JM, Kranz DM, Herbert AS, Procko E(2020) Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. Science. 369: 1261-5.
16. Hirano T, Murakami M (2020) COVID-19: a new virus, but a familiar receptor and cytokine release syndrome. Immunity. 52: 731-3
17. Clarke L, Fairley S, Zheng-Bradley X, Streeter I, Perry E, Lowy E, Tasse AM, Flicek P (2017) The international genome sample resource (IGSR): a worldwide collection of genome variation incorporating the 1000 genomes project data. Nucleic Acids Res. 45: D854-9.
18. Consortium, G.T., Laboratory, D.A., Coordinating Center -Analysis Working, G., Statistical Methods groups-Analysis Working, G., Enhancing, G.g., Fund, N.I.H.C., Nih/Nci, Nih/ Nhgri, Nih/Nimh, Nih/ Nida, Biospecimen Collection Source Site, N., Biospecimen Collection Source Site, R., Biospecimen Core Resource, V., Brain Bank Repository University of Miami Brain Endowment, B., Leidos Biomedical-Project, M., Study, E., Genome Browser Data, I., Visualization, E.B.I., Genome Browser Data, I., Visualization-Ucsc Genomics Institute, U.o.C.S.C., Lead, a., Laboratory, D.A., Coordinating, C., management, N.I.H.p., Biospecimen, c., Pathology, e, Q.T.L.m.w.g., Battle, A., Brown, C.D., Engelhardt, B.E., Montgomery, S.B, (2017) Genetic effects on gene expression across human tissues. Nature550: 204–13.
19. Mallick S, Li H, Lipson M, Mathieson I, Gymrek M, Racimo F, Zhao M, Chennagiri N, Nordenfelt S, Tandon A, Skoglund P, Lazaridis I, Sankararaman S, Fu Q, Rohland N, Renaud G, Erlich Y, Willems T, Gallo C, Spence JP, Song YS, Poletti G, Balloux F, van Driem G, de Knijff P, Romero IG, Jha AR, Behar DM, Bravi CM, Capelli C, Hervig T, Moreno-Estrada A, Posukh OL, Balanovska E, Balanovsky O, Karachanak-Yankova S, Sahakyan H, Toncheva D, Yepiskoposyan L, Tyler-Smith C, Xue Y, Abdullah MS, Ruiz-Linares A, Beall CM, Di Rienzo A, Jeong C, Starikovskaya EB, Metspalu E, Parik J, Villems R, Henn BM, Hodoglugil U, Mahley R, Sajantila A, Stamatoyannopoulos G, Wee JT, Khusainova R, Khusnutdinova E, Litvinov S, Ayodo G, Comas D, Hammer MF, Kivisild T, Klitz W, Winkler CA, Labuda D, Bamshad M, Jorde LB, Tishkoff SA, Watkins WS, Metspalu M, Dryomov S, Sukernik R, Singh L, Thangaraj K, Paabo S, Kelso J, Patterson N, Reich D (2016) The Simons genome diversity project: 300 genomes from 142 diverse populations. Nature 538: 201-6.
20. Rigat B, Hubert C, Alhenc-Gelas F, Cambien F, Corvol P, Soubrier F.J. (1990) An insertion/deletion polymorphism in the angiotensin I converting enzyme gene accounting for half the variance of serum enzyme levels. Clin Invest. 86: 1343-6.
21. Barley J, Blackwood A, Carter ND, Crews DE, Cruickshank JK, Jeffery S, Ogunlesi AO, Sagnella GA (1994) Angiotensin converting enzyme insertion/deletion polymorphism: association with ethnic origin. J Hypertens. 12: 955-7.
22. Cambien F (1994) The angiotensin-converting enzyme (ACE) genetic polymorphism: its relationship with plasma ACE level and myocardial infarction. Clin Genet. 46: 94-101.
23. Matsuda A, Kishi T, Jacob A, Aziz M, Wang P (2012) Association between insertion/deletion polymorphism in angiotensin-converting enzyme gene and acute lung injury/acute respiratory distress syndrome: a meta-analysis. BMC Med Genet. 13: 76.
24. Xu G, Fan G, Sun Y, Yu L, Wu S, Niu W (2018) Association of angiotensin-converting enzyme gene I/D polymorphism with chronic obstructive pulmonary disease: a meta-analysis. J Renin Angiotensin Aldosterone Syst. 19(2): 1470320318770546.
25. Li YF, Zhu XM, Liu F, Xiao CS, Bian YF, Li H, Cai J, Li RS, Yang XC (2012)Angiotensin-converting enzyme (ACE) gene insertion/deletion polymorphism and ACE inhibitor-related cough: a meta-analysis. PLoS One 7: e37396.
26. Troche MS, Brandimore AE, Okun MS, Davenport PW, Hegland KW (2014) Decreased cough sensitivity and aspiration in Parkinson disease. Chest. 146: 1294-9.
27. Morimoto S, Okaishi K, Onishi M, Katsuya T, Yang J, Okuro M, Sakurai S, Onishi T, Ogihara T (2002) Deletion allele of the angiotensin-converting enzyme gene as a risk factor for pneumonia in elderly patients. Am J Med. 112: 89-94.
28. Nie W, Zang Y, Chen J, Liu T, Xiao L, Xiu Q (2014) Angiotensin-converting enzyme I/D polymorphism is associated with pneumonia risk: a meta-analysis. J Renin Angiotensin Aldosterone Syst. 15: 585-92.
29. Fang L, Karakiulakis G, Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 8: 116-8.
30. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Solomon SD (2020) Renin-angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 382: 1653-9.
31. Ferrario CM, Jessup J, Chappell MC, Averill DB, Brosnihan KB, Tallant EA, Diz DI, Gallagher PE (2005) Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation. 111: 2605-10.
32. Chirag Bavishi C, Maddox TM, Messerli FH (2020) Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system llockers. JAMA Cardiol. 5: 745-7.

33. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, Wang Z, Li J, Li J, Feng C, Zhang Z, Wang L, Peng L, Chen L, Qin Y, Zhao D, Tan S, Yin L, Xu J, Zhou C, Jiang C, Liu L (2020) Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 63: 364-4.