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Genotype variation of *ACE* and *ACE2* genes affects the severity of COVID-19 patients

Ingrid Faustine[1,6†], Deli Marteka[1†], Amarila Malik[2*], Eko Supriyanto[3†] and Nadia F. Syafhan[4,5†]

Abstract

Objective Genetic polymorphisms in *ACE* and *ACE2* genes are involved in the RAS regulation of blood pressure and their activity may confer susceptibility to hypertension. In addition, they may play a role in SARS-CoV-2 pathogenesis and the severity of COVID-19. This study aims to determine the effect of genetic variations in the *ACE* (rs4331) and *ACE2* (rs2074192) genes with hypertension comorbidity on the severity of COVID-19 in the Indonesian population.

Result 186 patients were enrolled and assigned into the COVID-19 group (n = 95) and non-COVID-19 group (n = 91) in this cross-sectional study. GG genotype frequency was dominant in *ACE* gene, but there were no significant differences between the groups (p = 0.163). The two groups had a significant difference (p = 0.000) for the CC genotype frequency (0,37 vs. 0.01) in the *ACE2* gene. The proportion of women with COVID-19 is higher (51%), but men with hypertension had more severe symptoms (44%). Men with hypertension comorbidity, GG (*ACE*), and TT (*ACE2*) genotypes tended to have moderate-to-severe symptoms (25%). Similarly, women with hypertension as well as GG and CT genotypes tended to have moderate-to-severe symptoms (21%). We conclude that hypertension and mutations in the *ACE* (rs4331) and *ACE2* (rs2074192) genes affect the severity of COVID-19.

Keywords *ACE* gene, *ACE2* gene, rs4331, rs2074192, COVID-19, Indonesian population, Hypertension comorbide, rhAmp SNP genotyping

Introduction

To date, there have been 6.8 million cases of COVID-19 in Indonesia; 50.4% of them are women, and 48% have hypertension comorbidity, with a mortality rate of 2.4% [1], which is greater than the global mortality rate of 0.9% (May 2023) [2]. Most patients infected with SARS-CoV-2 were asymptomatic, but of the patients requiring hospitalization, 86% were classified as moderate and severe, with 17% of patients died [3].

The Renin-Angiotensin System (RAS) is a blood pressure regulatory pathways. It is known to be involved in the pathogenesis of COVID-19, in which SARS-CoV-2 uses Angiotensin-Converting Enzyme-2 (ACE2) as a receptor-binding agent to enter the cell [4]. Decreased ACE2 bioavailability and increased ACE activity level can increase the activity of Angiotensin-II (AngII) in RAS

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and may lead to COVID-19-induced inflammation and lung injury [5].

Genetic polymorphisms in *ACE* and *ACE2* genes have been shown to confer susceptibility to hypertension [6, 7]. In the pathogenesis of COVID-19, *ACE2* gene polymorphism located in X chromosome was postulated to cause a higher prevalence of COVID-19 in men [8]. Two rs numbers that were included in SNPs with a MAF greater than 10%, i.e., rs4331 and rs1799752 (I/D), as reported by Chung (2013) [9], were chosen to be analyzed in this study. However, our previous study in Indonesian population with COVID-19, which were type II dominant, showed inconsistent and inconclusive results (unpublished observations). Another study showed that the rs4331 polymorphisms were in linkage disequilibrium with the *ACE* I/D polymorphisms and were readily accessible by the rhAmp assay [10]. Therefore, we attempted to provide evidence of the effect of genetic variation of the rs4331 *ACE* gene and rs2074192 *ACE2* gene on the severity of COVID-19 in COVID-19 patients with hypertension comorbidity.

Materials and methods

Design and study participant

In this cross-sectional study, we collected participants from 18-year-old patients from health facilities located in Lahat District in South Sumatra Province, located in the Western part of Indonesia, and the city of Palu in Central Sulawesi Province, located in the Eastern part Indonesia, with a minimum sample size calculated using a predetermined formula. We collected anthropometric and clinical data from 95 COVID-19 participants who were positive for SARS-CoV-2 (nose or throat swab real-time-polymerase chain reaction (rt-PCR) test) who received treatment in a hospital or underwent self-isolation under the monitoring of a health facility. The COVID-19 severity category is based on our preliminary research, which refers to the NIH guidelines [3, 11]. We also selected 91 non-COVID-19 populations from outpatient clinics without matching age or sex for the baseline group. Another inclusion criterion is that the participants should have no previous history of COVID-19 diagnosis based on a positive rtPCR test for the SARS-CoV-2 virus. History of hypertension comorbidity was obtained from the participant's medical records.

Genotyping of SNP by rhAmp SNP Genotyping

Genomic DNA was extracted from whole blood using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) and measured using a NanoDrop™ One Microvolume UV–Vis Spectrophotometer (Thermo Fisher Scientific, Waltham, MA). DNA was diluted to a concentration of 2 ng/μL. One *ACE* SNP (rs4331; A/G) Exon 15 and one *ACE2* SNP (rs2074192; C/T) intron 16 were identified by the rhAmp SNP genotyping method according to the rhAmp SNP protocol [12]. The PCR conditions were as follows: enzyme activation at 95 °C for 10 min, followed by 40 cycles of denaturation at 95 °C for 10 s, annealing at 60 °C for 30 s, extension at 68 °C for 20 s, ending with heat inactivation at 99.9 °C for 15 min. Quality control is always performed during laboratory work, where gBlock and NTC are used as positive and negative controls, respectively. Amplification was performed using AriaMx RT-PCR (Agilent, Santa Clara, US). AriaMx software was used to generate allele calls and allele discrimination plots automatically.

Statistical analysis

Population genetic data was analyzed using the Hardy-Weinberg equilibrium principle with the online software SNPStats (https://www.snpstats.net/). Categorical variables were expressed as amounts and percentages. Differences between groups were evaluated using Fisher's exact or Chi-square test, depending on sample size and multiple comparison corrections with Bonferroni correction. We used SPSS version 21.0 (IBM Corp., Armonk, NY, USA) for all statistical analysis. We used two-tailed *p*-values in our analysis with a $p<0.05$ level of significance.

Result

Distribution of genetic variation of *ACE* and *ACE2* genes

One-hundred eighty-six participants were recruited and divided into COVID-19 groups and non-COVID-19 groups. The frequency of the GG genotype *ACE* gene rs4331 and CT genotype *ACE2* gene rs2074192 were dominant in both the COVID-19 and non-COVID-19 groups (Fig. 1A). No significant difference was observed in the proportion of *ACE* gene genotypes (p=0.163), whereas in the *ACE2* gene, a significant difference was observed in the proportion of genotypes (p=0.000), in which CC genotype poses more risk for COVID-19 compared to the non-COVID-19. Of the total sample, there were 49% of non-COVID-19 patients and 51% of COVID-19 patients, but based on sex, there was no significant difference between the two groups (p=0.544) (Fig. 1B). When comparing sexes, the percentage of GG genotypes *ACE* gene in men was found to higher than in women. In contrast, in the *ACE2* gene, the TT genotype was found more in men (2%) and absent in women, and women in the COVID-19 group were more likely to have the CT genotype (Fig. 1C).

Association of clinical characteristics with the severity of COVID-19

We then analyzed the data to determine the associations between clinical characteristics and the severity by sex in the COVID-19 group. As shown in Table 1, there were no differences in terms of age, hypertension comorbid, BMI,

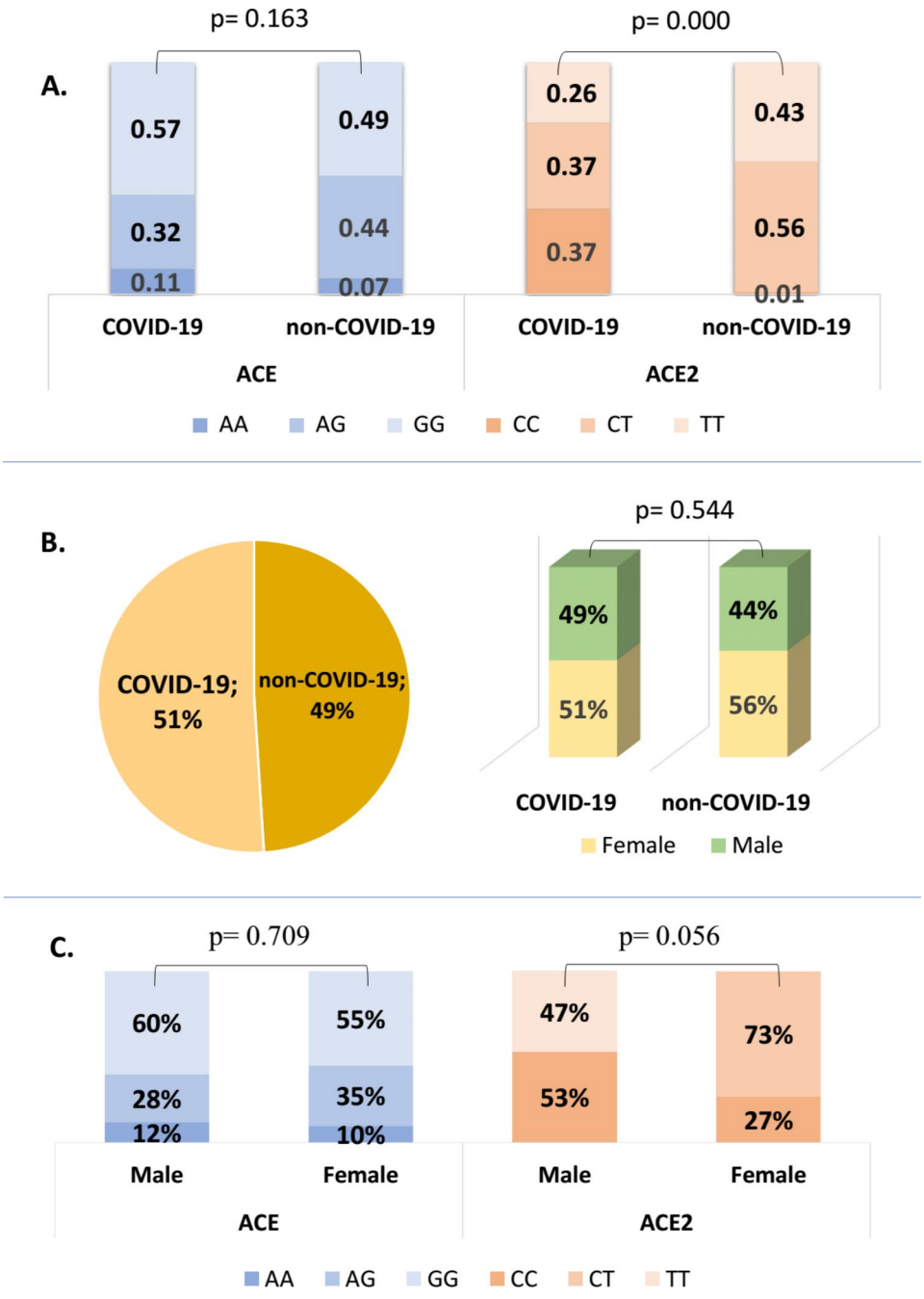

Fig. 1 Genotype distribution of *ACE* and *ACE2* genes in COVID-19. Figure 1 A Genotype frequency of *ACE* and *ACE2* in the non-COVID-19 and COVID-19 groups. Figure 1B shows the percentages of COVID-19 and non-COVID-19 groups, and percentages of sex of each group. Figure 1 C shows the percentage of each genotype by sex in the COVID-19 group

type of care, and length of stay for both male and female with mild and moderate-to-severe COVID-19 ($p>0.05$). However, of the eleven symptoms recorded (Suppl. Table 1), we found that anosmia and vomiting were dominant in women with moderate-to-severe COVID-19 ($p<0.05$).

Genetic variation of *ACE* and *ACE2* on comorbidities, sex, and severity of COVID-19

We noted that 28 (29%) participants had hypertension, and 67 (70%) were without hypertension. An assessment of the effect of genetic variations on hypertension, sex, and the severity of COVID-19 is presented in Fig. 2. In the hypertension group, men with hypertension comorbidity and GG and TT genotypes tended to have

Table 1 Clinical characteristics of severity COVID-19 by sex

Variables	Mild		p-value	Moderate-Severe		p-value
	Male (n = 20)	Female (n = 20)		Male (n = 27)	Female (n = 28)	
Age (y)			0.403			0.435
18–39	6 (30%)	10 (50%)		8 (30%)	10 (36%)	
40–59	12 (60%)	8 (40%)		14 (52%)	16 (57%)	
≥ 60	2 (10%)	2 (10%)		5 (18%)	2 (7%)	
Hypertension Comorbidity	3 (15%)	4 (20%)	0.500	12 (44%)	9 (32%)	0.509
BMI (Overweight-to-Obese)	9 (45%)	11 (55%)	0.752	16 (36%)	16 (57%)	1.000
Symptoms						
Anosmia	12 (60%)	10 (50%)	0.751	1 (4%)	14 (50%)	0.000
Vomiting	4 (20%)	4 (20%)	0.653	1 (4%)	8 (29%)	0.014
Treatment						
Hospital Admission	9 (45%)	4 (20%)	0.088	27 (100%)	27 (96%)	0.509
Self-isolation	11 (55%)	16 (80%)		0 (0%)	1 (4%)	
LoS (> 13 days)	10 (50%)	15 (75%)	0.191	4 (15%)	10 (36%)	0.142

BMI (Body Mass Index), LoS (Length of Stay)

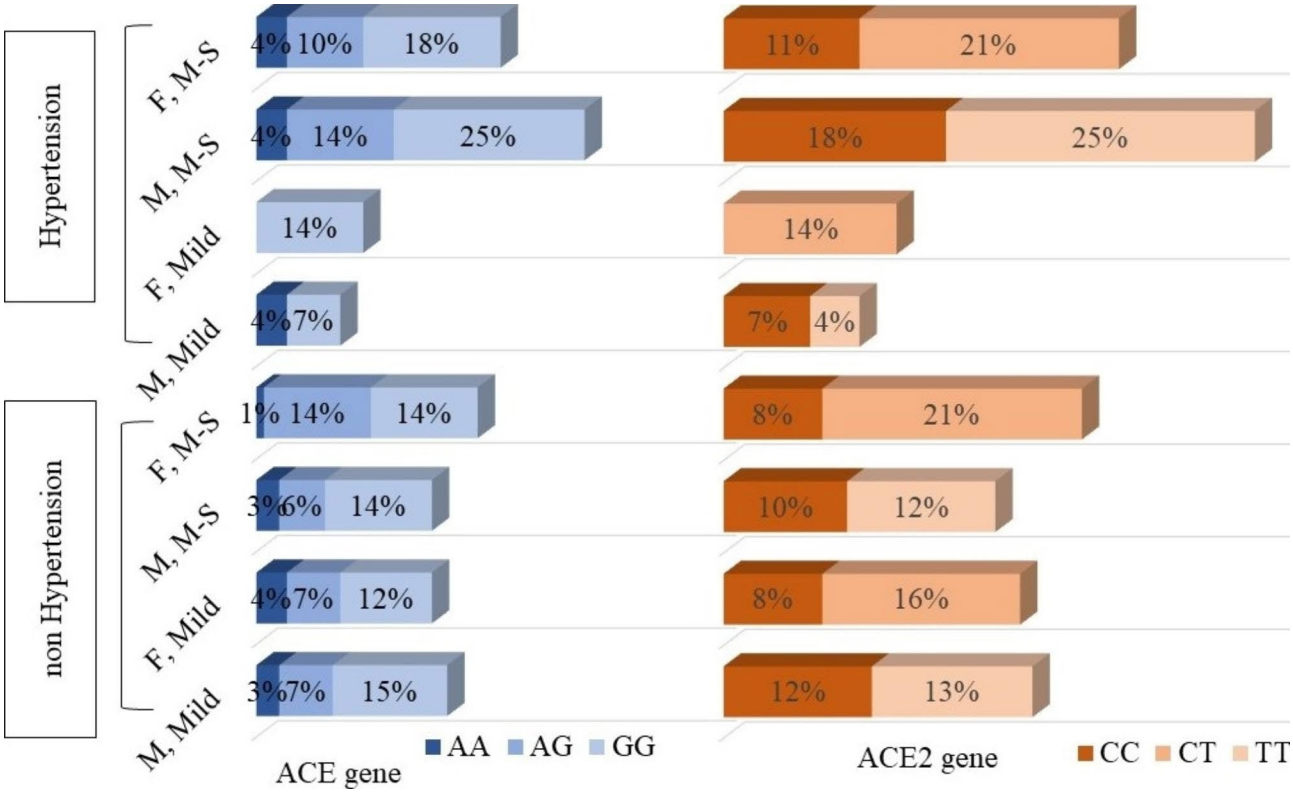

Fig. 2 The effect of genetic variations on hypertension comorbidity, sex, and the severity of COVID-19. The GG and TT genotype groups in men with hypertension comorbidity had the highest percentage of moderate-to-severe COVID-19. F (Female), M (Male), M-S (Moderate-to-Severe)

moderate-to-severe symptoms (25%). On the other hand, the non-hypertensive group comprised mostly of women without hypertension comorbidity or with CT genotype.

Discussion

Several studies have investigated the role of *ACE* and *ACE2* gene polymorphisms in COVID-19 susceptibility and disease severity [13–15]. ACE2 is a SARS-CoV-2 receptor, while ACE plays a role in blood pressure regulation. Functional variants that increase *ACE* and *ACE2* gene expression were thought to cause high viral binding to membrane sites, increasing carrier susceptibility to infection. Our previous study concluded that the rs4331 genotype showed consistent results, i.e., allele A was always found in samples with deletions and allele G with insertions (unpublished observations). These results

confirm that rs4331 can be used to detect I/D polymorphisms. Our results show that the COVID-19 group tended to carry the GG genotype in the *ACE* gene and the CT genotype in *ACE2*. A study by Jacob (2021) found that the insertion of *ACE* gene increases the expression level of *ACE2* [16]. Increased expression of ACE2 may increase the risk of viral infection and the detrimental effects of *ACE*2 on the lungs and other organs. At the same time, it increases ACE activity in the Ang II/AT1R response [17].

The *ACE2* gene in the X chromosome may be detrimental in men because it carries only one copy of the X-linked *ACE2* gene. However, our study found a more significant proportion of women than men in the COVID-19 group and non-COVID-19. In addition, we found that carriers of the *ACE2* genotype were more susceptible to COVID-19 events. In the COVID-19 group, we found that CC carriers tend to be male, while women tend to be CT genotype carriers. In addition, we only found the TT genotype in males. This result aligns with a study by Patel (2012), which showed that males were dominant carriers of CC, and the proportion of TT genotypes was higher in males than in females [18]. In addition, Suleiman (2021) also concluded that the dominant Asian female population carries the CC or CT genotype without appreciable differences between males and females, compared to those observed in Caucasians [19].

Mutations in *ACE2* and *ACE* can cause an increase in serum levels and expression of ACE2 [20]. Kamyshnyi (2020) stated that men have higher ACE2 expression levels than women, and Asian populations have higher ACE2 transcript levels than Caucasian and African populations [21]. RAS imbalance due to increased ACE2 expression in the lungs facilitates inflammation and coagulation processes due to Ang-II overproduction and Ang-[1–7] deficiency. On the other hand, SARS-CoV-2 has an intrinsically high affinity for the ACE2 receptor, and mild or moderate ACE2 deficiency cannot play a protective role in host defense against viral invasion [17, 22]. Our results show that hypertension comorbidity in men is associated with a greater severity of COVID-19-induced ACE2 deficiency.

The SNPs rs4331 of the *ACE* and rs2074192 of the *ACE2* genes investigated in our study were in exonic (synonymous) and intronic positions. However, mutations occur in introns that alter mRNA splicing and affect gene expression and protein levels at ACE2 levels [23, 24]. As observed in our study, the genotype of the mutant in the *ACE* gene, i.e., GG and in the *ACE2* genes, i.e., TT for men and CT for women, are associated with the risk prevalence and severity of SARS-CoV-2 infection. These results are similar to those reported by Hubacek (2021) and Hamet (2021), in which they showed that mutations in the *ACE* and *ACE2* genes were directly proportional to the severity of COVID-19 [25, 26]. In addition, the effects of ACE and ACE2 on blood pressure were reported; ACE2 reduces the vasoconstrictor angiotensin II and activity of ACE/AT1R in RAS. In addition, it was assumed that genetic variations that increase the expression or activity of ACE and ACE2 might contribute to cardiovascular disease and SARS-CoV-2 infection [27].

However, the molecular mechanisms behind these observations are still minimally elucidated [21, 28]. We must also consider variants in other gene regions related to gene expression and protein level to also be involved in increasing severity of COVID-19. In conclusion, hypertension and mutations in the *ACE* (rs4331) and *ACE2* (rs2074192) genes can cause greater severity in COVID-19 patients; therefore, special attention and prompt treatment is needed in the clinical management of COVID-19 patients with hypertension.

Limitations

Our study uses data from only two regions of Indonesia which were not affected by COVID-19 Delta cases. However, these two populations represent a geographic area with a high percentage of people with hypertension and deaths from COVID-19. Adjustments for potentially confounding variables, such as vaccination stage factors and hypertension therapy, may contribute to differences in COVID-19 severity profiles. Our results suggest that evaluating genetic variation in *ACE* and *ACE2* genes can be a useful new diagnostic approach for clinical assessment and risk management of COVID-19 with hypertension.

Abbreviations

ACE	Angiotensin Converting Enzyme
ACE-2	Angiotensin Converting Enzyme-2
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
COVID-19	Corona Virus Disease 2019
SNP	Single Nucleotide Polymorphism
RAS	Renin-Angiotensin System
I/D	Insertion/deletion
rtPCR	Real-time-polymerase chain reaction

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13104-023-06483-z.

Supplementary Material 1

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Authors' contributions

IF: prepared the data, performed the experiments, analyzed and interpreted the results, and wrote the paper. DM: collected the data, performed the experiments. AM: conceived and designed the study, interpreted the results, and wrote the manuscript. ES and NFS: contributed to the study design.All authors read and approved the final manuscript.

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Data Availability
The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Declarations

Ethics approval and consent to participate
The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Tadulako University (Palu, Indonesia) and the Ethics Committee of the University of Indonesia Hospital (Depok, Indonesia) reference numbers 7916/UN.28.1.30/KL/2020 and 0058/SKPE/KKO/2021/ 00. Patients/participants were aware of the study's aims, risks, and benefits and provided their written informed consent to participate.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Peta Sebaran COVID-19. 2023. Available at: https://covid19.go.id/peta-sebaran-covid19. Accessed on 20th May 2023.
2. WHO Coronavirus (COVID-19) Dashboard. 2023. Available at: https://covid19.who.int/table. Accessed on 20th May 2023.
3. Faustine I, Malik A, Andrajati R, Wanandi SI. Clinical characteristics and Severity Profile of COVID-19 patient with hypertension in Palu, Central Sulawesi. Indones J Pharm. 2021;32(4):563–72. https://doi.org/10.22146/ijp.2729.
4. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: emergence, transmission, and characteristics of human coronaviruses. 2020; https://doi.org/10.1016/j.jare.2020.03.005.
5. Chappell MC, Marshall AC, Alzayadneh EM, Shaltout HA, Diz DI. Update on the angiotensin converting enzyme sex differences, and intracellular pathways. 2014;4(January):1–13.
6. Luo Y, Liu C, Guan T, Li Y, Lai Y, Li F, et al. Association of ACE2 genetic polymorphisms with hypertension-related target organ damages in south Xinjiang. Hypertens Res. 2019;42(5):681–9. https://doi.org/10.1038/s41440-018-0166-6.
7. Lozano-Gonzalez K, Padilla-Rodríguez E, Texis T, Gutiérrez MN, Rodríguez-Dorantes M, Cuevas-Córdoba B, et al. Allele frequency of ACE2 Intron Variants and its association with blood pressure. DNA Cell Biol. 2020;39(11):2095–101.
8. Gómez J, Albaiceta GM, García-clemente M, López-larrea C. Angiotensin-converting enzymes (ACE, ACE2) gene variants and COVID-19 outcome. Gene J. 2020;762:145102. https://doi.org/10.1016/j.gene.2020.145102.
9. Chung CM, Wang RY, Fann CSJ, Chen JW, Jong YS, Jou YS, et al. Fine-mapping angiotensin-converting enzyme gene: separate QTLs identified for hypertension and for ACE activity. PLoS ONE. 2013;8(3):e56119. https://doi.org/10.1371/journal.pone.0056119.
10. Faustine I, Malik A, Andrajati R, Wanandi SI. Detection of ACE Gene SNPs Using rhAmp Genotyping Platform and Their Association with I/D Polymorphism in COVID-19 Patients with Hypertension. Indones J Pharm. 2023; In Press.
11. Health NIof. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. Vol. 2019, Nih. 2020. 130 p. Available at: https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed on 21st May 2021.
12. Integrated DNAT. Inc. Rhamp-Snp-Genotyping. Idt_Protocol. 2017. Available at: https://https://www.idtdna.com/pages/products/qpcr-and-pcr/genotyping/rhamp-snp-genotyping/master-mix-and-reporter-mixes. Accessed on 1st April 2021.
13. Martínez-Gómez LE, Herrera-López B, Martinez-Armenta C, Ortega-Peña S, Camacho-Rea M, del C, Suarez-Ahedo C, et al. ACE and ACE2 gene variants are Associated with severe outcomes of COVID-19 in Men. Front Immunol. 2022;13(February):1–10.
14. Íñiguez M, Pérez-Matute P, Villoslada-Blanco P, Recio-Fernandez E, Ezquerro-Pérez D, Alba J, et al. ACE gene variants rise the risk of severe COVID-19 in patients with hypertension, dyslipidemia or diabetes: a spanish pilot study. Front Endocrinol (Lausanne). 2021;12(August):1–11. https://doi.org/10.3389/fendo.2021.688071.
15. Gunal O, Sezer O, Ustun GU, Ozturk CE, Sen A, Yigit S, et al. Angiotensin-converting enzyme-1 gene insertion/ ACE gene variants rise the risk of severe COVID-19 in patients with hypertension, dyslipidemia or diabetes deletion polymorphism may be associated with COVID-19 clinical severity: a prospective cohort study. Ann Saudi Med. 2021;41(3):141–6. https://doi.org/10.5144/0256-4947.2021.141.
16. Jacobs M, Lahousse L, Van Eeckhoutte HP, Wijnant SRA, Delanghe JR, Brusselle GG, et al. Effect of ACE1 polymorphism rs1799752 on protein levels of ACE2, the SARS-CoV-2 entry receptor, in alveolar lung epithelium. ERJ Open Res. 2021;7(2):1–4. https://doi.org/10.1183/23120541.00940-2020.
17. Ni W, Yang X, Yang D, Bao J, Li R, Xiao Y, et al. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Crit Care. 2020;24(422):1–10. https://doi.org/10.1186/s13054-020-03120-0.
18. Patel SK, Wai B, Ord M, MacIsaac RJ, Grant S, Velkoska E, et al. Association of ACE2 genetic variants with blood pressure, left ventricular mass, and cardiac function in caucasians with type 2 diabetes. Am J Hypertens. 2012;25(2):216–22. https://doi.org/10.1038/ajh.2011.188/nature06264.
19. Suleiman A, Rafaa T, Alrawi A, Dawood M. The impact of ACE2 genetic polymorphisms (rs2106809 and rs2074192) on sex susceptibility to COVID-19 infection and recovery: a systematic review. Baghdad J Biochem Appl Biol Sci. 2021;2(03):167–80. https://doi.org/10.47419/bjbabs.v2i03.53.
20. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. Sci (80-). 2020;367(6485):1444–8. https://doi.org/10.1126/science.abb2762.
21. Kamyshnyi A, Krynytska I, Matskevych V, Marushchak M, Lushchak O. Arterial hypertension as a risk comorbidity associated with covid-19 pathology. Int J Hypertens. 2020;2020. https://doi.org/10.1155/2020/8019360.
22. Alimoradi N, Sharqi M, Firouzabadi D, Sadeghi MM, Moezzi MI, Firouzabadi N. SNPs of ACE1 (rs4343) and ACE2 (rs2285666) genes are linked to SARS-CoV-2 infection but not with the severity of disease. Virol J. 2022;19(1):1–9. https://doi.org/10.1186/s12985-022-01782-6.
23. Hesselberth JR. Lives that introns lead after splicing. Wiley Interdiscip Rev RNA. 2013;4(6):677–91. https://doi.org/10.1002/wrna.1187.
24. Persu A, Lambert M, Deinum J, Cossu M, Visscher N, De, Minon J et al. A Novel splice-site mutation in angiotensin I-Converting causes a dramatic increase in circulating ACE through deletion of the Transmembrane Anchor. 2013;8(4). https://doi.org/10.1371/journal.pone.0059537.
25. Hamet P, Pausova Z, Attaoua R, Hishmih C, Haloui M, Shin J, et al. SARS-CoV-2 receptor ACE2 gene is Associated with Hypertension and Severity of COVID 19: Interaction with sex, obesity, and smoking. Am J Hypertens. 2021;34(4):367–76. https://doi.org/10.1093/ajh/hpaa223.
26. Hubacek JA, Dusek L, Majek O, Vaclav Adamek TC, Dlouha D, Adamkova V. ACE I/D polymorphism in czech first-wave SARS-CoV-2-positive survivors. Clin Chim Acta. 2021;519(January):206–9. https://doi.org/10.1016/j.cca.2021.04.024.
27. Sabater Molina M, Nicolás Rocamora E, Bendicho AI, Vázquez EG, Zorio E, Rodriguez FD, et al. Polymorphisms in ACE, ACE2, AGTR1 genes and severity of COVID-19 disease. PLoS ONE. 2022;17(2):e0263140. https://doi.org/10.1371/journal.pone.0263140.
28. Gemmati D, Tisato V. Genetic hypothesis and pharmacogenetics side of renin-angiotensin-system in COVID-19. Genes (Basel). 2020;11(9):1–17. https://doi.org/10.3390/genes11091044.

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