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Due Date: 31 August 2025

ISSN 2580-9296 (ONLINE)

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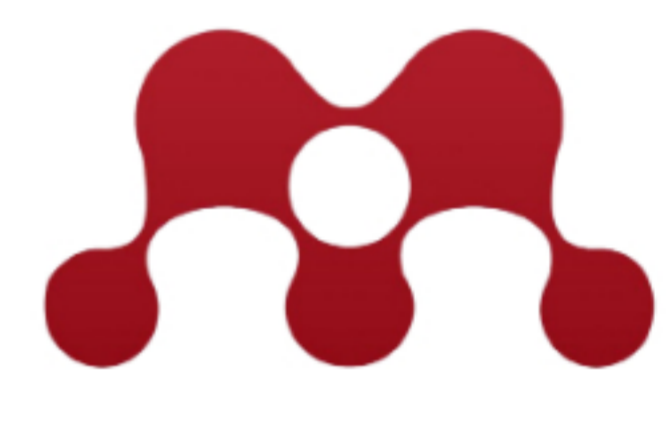
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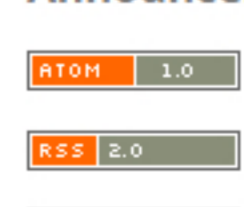
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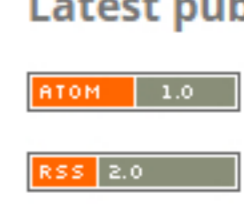
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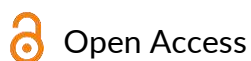


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Angiotensin Converting Enzyme 2 (ACE2) G8790A Gene Polymorphism as a Risk Factor for Essential Hypertension

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DOI: [10.35898/ghmj-82s1231](https://doi.org/10.35898/ghmj-82s1231)

ABSTRACT

Background: Globally, the number of people with hypertension has doubled, from 650 million to 1.3 billion. The World Health Organization reported that hypertension is responsible for more than 10 million deaths every year. Essential hypertension is a multifactorial condition with genetics as one of the factors. Genome-Wide Association Study has identified several genes associated with hypertension, one of which is the Angiotensin Converting Enzyme 2 (ACE2) gene. Essential hypertension may be predisposed to by the G8790A polymorphism of the ACE2 gene, which is hypothesized to interfere with the normal function of the Renin Angiotensin System (RAS).

Aims: The purpose of this study is to determine whether the ACE2 G8790A gene polymorphism in Cirebon, West Java, Indonesia, is associated with an increased risk of essential hypertension.

Methods: This is a case-control study conducted at the Talun Health Center, Cirebon Regency, April-August 2024, involving 30 essential hypertensive patients and 30 healthy controls. The study population comprised adults aged 30 to 72 years. Data was obtained through the examination of blood pressure, DNA extraction, PCR-RFLP with ALUI restriction enzyme, and then visualization of the results with Gel Electrophoresis. The Chi-Square Test technique and the Odds Ratio (OR) computation were used to analyze the data.

Results: The G allele was higher in the case group 33 (55%), while the A allele was higher in the control group 34 (56.7%). The statistical analysis showed that there was no significant link between the ACE2 G8790A gene variation and essential hypertension, with a p-value of 0.592 ($p > 0.05$) (OR = 0.750; CI = 0.262–2.151).

Conclusion: The ACE2 gene G8790A polymorphism and the rate of hypertension in Cirebon, West Java, were not significantly correlated. Further research is required on a larger scale to investigate the effects of gene combinations or interactions with other locus genes on essential hypertension.

Keywords: ACE2 gene; G8790A Polymorphism; Essential hypertension.

Received: 10 July 2025

Reviewed: 14 July 2025

Revised: 27 July 2025

Accepted: 15 August 2025.

1. Introduction

Hypertension is a dangerous condition that can lead to major side effects like heart attack, stroke, retinopathy, and renal failure (Unger et al., 2020). It is occurred when the systolic blood pressure (SBP) rises by more than 140 mmHg and/or the diastolic blood pressure (DBP) rises by more than 90 mmHg (Kemenkes, 2021). The Update JNC-8 Guideline Recommendation divides hypertension into two categories: primary hypertension (90% of the cases), which people have an unknown etiology, and secondary hypertension (10% of the cases), which people have a known cause for their high blood pressure (Olin & Pharm, 2018). Since hypertension typically has no symptoms, it is known as the "silent killer" because most people are unaware of their illness until they have clinical difficulties such as kidney damage, heart failure, stroke, heart attack, and many other health issues. (P2PTM Kemenkes RI, 2024). Globally, there are now 1.3 billion hypertensive individuals, up from 650 million previously (Zhou et al., 2021). Over 10 million fatalities are attributed to hypertension each year, more than all other health risks combined, according to the World Health Organization (WHO) (World Health Organization, 2023). With a prevalence of 34.1% among those over the age of 18, West Java is now the second-highest area (Kemenkes RI, 2018). The estimated number of hypertension patients in Cirebon Regency in 2021 is 648,030, and 73,173, or 11.3% of the total number of hypertension patients, have received medical treatment according to standards (Dinas Kesehatan Kabupaten Cirebon, 2021). Essential hypertension is a manifestation of the presence of hemodynamic imbalance of the cardiovascular system, the cause of which is multifactorial, including relating to genetic factors, the environment, and the centers of regulation of hemodynamics (Alwi, 2014).

Patients with essential hypertension often experience a wide range of symptoms, including headache, irregular heartbeat, visual abnormalities, chest discomfort, nausea, vomiting, and convulsions. Nowadays, a digital blood pressure monitor is used to take three readings of blood pressure at 5-minute intervals in order to detect essential hypertension. The patient will have an ECG and blood glucose tests after being diagnosed with high blood pressure to rule out diabetes and other cardiovascular diseases. Treatments for essential hypertension include angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and beta-blockers.

Age, sex, and genetics are unmodifiable risk factors for hypertension; risk variables that can be modified include smoking, a low-fiber diet, dyslipidemia, excessive salt intake, a sedentary lifestyle, stress, obesity, and alcohol use (P2PTM Kemenkes RI, 2024). In most genetic research related to hypertension, The renin-angiotensin system (RAS), one of the physiological systems that controls blood pressure, is the source of the candidate genes (Lu et al., 2012). Renin-Angiotensin-Aldosterone System (RAAS) genes, such as those involved in making aldosterone, ACE2, ACE, and others, are linked to a higher risk of hypertension. Furthermore, there is a correlation between the ACE2 gene and essential hypertension, diabetes mellitus, coronary heart disease, and the severity of COVID-19. These studies include findings from Pan (2023), Yan et al. (2008), M. Yang, Zhao, Xing, and Shi (2015), and Younas, Ijaz, and Choudhry (2022).

The ACE2 gene manufactures the protease enzyme Angiotensin Converting Enzyme 2, which sticks to the surface of cell membranes in the heart, blood vessels, kidneys, intestines, testicles, and lungs (Chappell, Marshall, Alzayadneh, Shaltout, & Diz, 2014). This gene has 805 amino acids and is located on the Xp22.2 chromosome (ACE2 Gene, 2023). ACE2 is an ACE homologue that maintains blood pressure homeostasis by regulating negative RAS, which maintains a balance between vasoconstrictor and vasodilator actions (Burrell, Johnston, Tikellis, & Cooper, 2004). The G8790A gene polymorphism of ACE2 is a restriction enzyme truncation site located in the fourth base of the third intron adjacent to the exon and shows that this locus can alter the alternative splicing of mRNA and affect ACE2 gene expression. The G8790A gene polymorphism of ACE2 causes changes in the amount of Ang serum (1–7) that functions to inhibit vasoconstriction, which can lead to increased blood pressure (Li, 2012). Blood pressure is currently associated with genetic causes. Many polymorphisms that raise an individual's risk of acquiring high blood pressure have been found by researching genes that produce monogenic forms of hypertension and pathways related to blood pressure regulation (Lupton, Chiu, & Lind, 2011). There is no recent research on the ACE2 G8790A Gene Polymorphism being a risk factor for high blood pressure in Cirebon, West Java, Indonesia. This study was conducted to determine whether the ACE2 G8790A gene polymorphism in Cirebon, West Java, is associated with an increased risk of essential hypertension.

2. Methods

Study design and Research procedures

An analytical study was carried out at the Talun Health Center in Cirebon Regency from April to August 2024 to examine the link between essential hypertension and the G8790A gene variation of the Angiotensin Converting Enzyme 2 (ACE2). Participants were selected using purposive sampling according to established inclusion and exclusion criteria. The case-control study identified a sample size of 60 participants, with 30 individuals in the case group and 30 individuals in the control group.

Inclusion criteria for the case group included (1) a diagnosis of essential hypertension based on the updated eighth Joint National Committee (JNC-8) Guideline Recommendations and (2) a family history of hypertension. The exclusion criteria include (1) patients who are pregnant or lactating, and (2) patients with hypertension who also have diabetes, kidney disease, liver disease, stroke, or other cardiovascular disease. The control group's members fit the same inclusion and exclusion criteria as the case group, and they were diagnosed as non-hypertensive based on the same diagnostic standards. Control subjects were matched to case subjects based on age (± 2 years). To minimize bias, patients who were pregnant or breastfeeding or had a history of diabetes mellitus, renal disease, coronary heart disease, or other cardiovascular diseases were excluded from the case group (Kuswara et al., 2024). The researchers collected demographic data and measured the blood pressure of all study subjects throughout the study.

Measurement

Blood samples were collected from the peripheral vein. The samples were thereafter kept at ambient temperatures in tubes treated with EDTA. Participants who fulfilled the research criteria were evaluated by a questionnaire administered by a physician to ensure accurate data entry. Clinical characteristics gathered during screening include age, gender, and familial history of hypertension. Additionally, blood pressure was assessed three times, with an interval of 3 to 5 minutes between each test. Blood samples (3–5 cc) were obtained at the Talun Public Health Centre, transferred to EDTA tubes, and transferred to the Research Laboratory at Universitas Swadaya Gunung Jati Cirebon for genetic analysis. DNA from leukocytes was extracted using the QIAamp kit (Qiagen, Tokyo, Japan) following the recommended protocol.

Instruments

The gene polymorphisms were amplified using the restriction fragment length polymorphism (RFLP) and polymerase chain reaction (PCR) techniques. The amplification process contained 12.5 μ l of PCR Taq Master Mix, 1.0 μ l of upstream and downstream primers, 1.0 μ l of DNA template, and 9.5 μ l of deionized water, for a total volume of 25 μ l. We used PCR-RFLP for ACE2 G8790A, using the forward primer 5'-CATGTGGTCAAAGGATATCT-3' and the reverse primer 5'-AAAGTAAGGTTGGCAGACAT-3'. The following conditions were used for the PCR: 5 minutes of pre-denaturation at 94°C, 32 cycles of denaturation at 94°C for 40 seconds, 30 seconds of annealing at 58°C, 30 seconds of extension at 72°C, and 5 minutes of terminal extension at 72°C. The ACE2 G8790A PCR products were subjected to a water bath reaction with Alul endonuclease at 37°C for 3–16 hours. The resulting mixture was then electrophoresed on a 1.5% agarose gel and stained with 1.0 μ l gel red/ethidium bromide. A UV analyzer was used to determine genetic polymorphism.

Statistical Analysis

With the essential hypertension serving as the dependent variable and the ACE2 G8790A gene polymorphism serving as the independent variable, univariate analysis is used to characterize the study sample by displaying the frequency distribution of each study variable. The Chi-Square test is used to compare results in bivariate analysis, including category variables. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to evaluate the risk associated with variables including genotype, allele frequency, and the presence of gene polymorphism, with significance established at $p < 0.05$.

Ethical Clearance

The Ethics Committee of the Faculty of Medicine at Universitas Swadaya Gunung Jati in Cirebon, Indonesia, authorized the study protocol and ensured that it adhered to the 1975 Declaration of Helsinki and its revisions' ethical guidelines. Each patient signed a written informed consent form prior to the study. Prior to enrollment, written informed permission was obtained from each patient. For patients who were younger than 18, written agreement was acquired from their parents or legal guardians.

3. Results

Respondent characteristics

In **Table 1**, it can be seen that all research subjects were 60 people. The matching process between the case group and the control group resulted in no differences in the frequency distribution of gender and age among the research subjects. The frequency distribution of characteristics in the case group who had a family history of hypertension was 19 subjects (63.3%), and who did not have a family history of hypertension was 11 subjects (36.7%), while in the control group who had a family history of hypertension was 3 subjects (10%), and who did not have a family history of hypertension was 27 subjects (90%).

Table 1. Participant's demographic information

Characteristics	Case		Control	
	n	%	n	%
Age				
<45	8	26.7%	8	26.7%
>45	22	73.3%	22	73.3%
Total	30	100%	30	100%
Sex				
Male	15	50.0%	15	50.0%
Female	15	50.0%	15	50.0%
Total	30	100%	30	100%
Family History of Hypertension				
Yes	19	63.3%	3	10%
No	11	36.7%	27	90%
Total	30	100%	30	100%

Genotypic Data

In the case group, the genotype distribution for ACE2 G8790A is GG 12 (40%), GA 9 (30%), and AA 9 (30%). In the control group, the genotype distribution is GG 10 (33.3%), GA 6 (20%), and AA 14 (46.7%). The G allele distribution in the case group is 33 (55%) and 26 (80%) within the control group, while the A allele distribution is 27 (45%) in the case group and 34 (56.7%) in the control group. P-value for genotype ($p=0.393$) and allele ($p=0.201$) did not show significance (**Table 2**).

Table 2. Genotype and allele distribution for ACE2 G8790A

Variables	Case (n=30)	Control (n=30)	p-values
Genotype	n%	n%	
GG	12(40%)	10(33.3%)	0.393 ^a
GA	9(30%)	6(10%)	
AA	9(30%)	14(46.7%)	
Allele			
G	33(55%)	26(43.3%)	0.201 ^a
A	27(45%)	34(56.7%)	

^aChi-square test

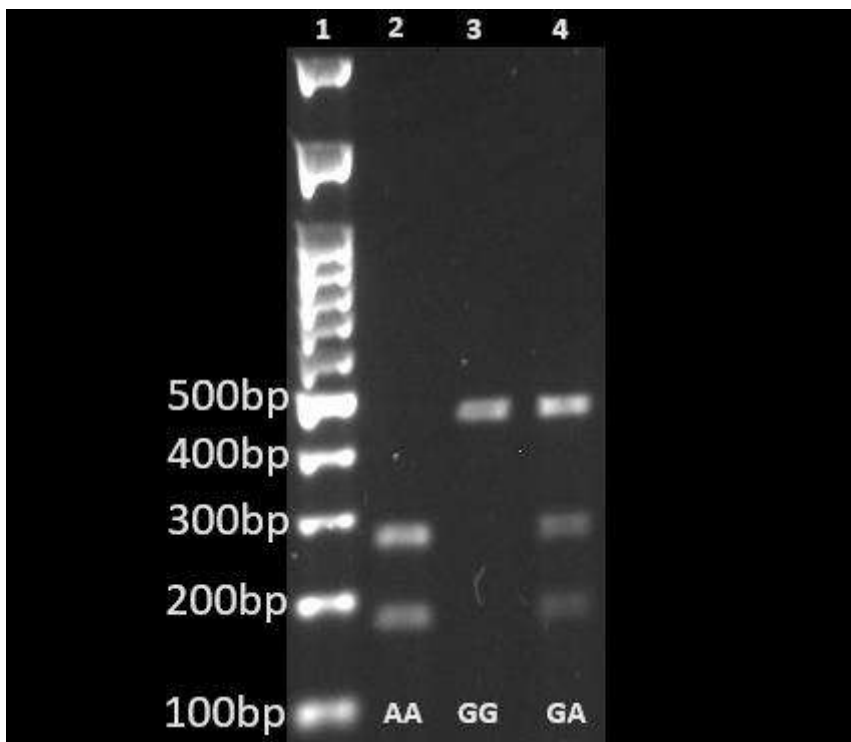


Figure 1. PCR-RFLP product of ACE2 G8790A polymorphism on an agarose gel, digestion outcome: Lane (1) DNA marker; (2) AA=281 bp+185 bp; (3) GG=466 bp; and (4) GA=466 bp+281 bp+185 bp

Bivariate analysis

Bivariate analysis results indicated that the prevalence of polymorphisms was greater in the control group, with 20 subjects (66.7%), compared to the case group, which comprised 18 subjects (60%). The adjusted Chi-Square Test (Pearson Chi-Square) yielded a p-value of 0.592 ($p > 0.05$), indicating no significant association between the ACE2 G8790A gene polymorphism and the occurrence of essential hypertension. Further analysis yielded an odds ratio (OR) of 0.750, indicating that individuals with the ACE2 G8790A gene polymorphism are not at significant risk for developing essential hypertension and have a protective factor 25% greater than those without the ACE2 G8790A gene polymorphism ($p = 0.592$; $OR = 0.750$; $CI = 0.262-2.151$).

Table 3. The polymorphism of ACE2 G8790A and essential hypertension

Polymorphism ACE2 G8790A	Case group	Control group	p-values	OR (95%CI)
	n%	n%		
Polymorphism +	18(60%)	20(66.7%)	0.592 ^a	0.750 (0.262- 2.151)
Polymorphism -	12(40%)	10(33.3%)		

^a Pearson Chi-Square Test

4. Discussion

Many genes, environmental factors, and their interactions influence the complex aetiology of essential hypertension. Its exact mechanism of action is still unknown. According to studies, the RAAS is crucial for blood pressure management, maintaining the proper balance of water and salt in the body, and modifying the tissues in the cardiovascular system (Y. L. Yang et al., 2015). The RAAS system may be negatively regulated by ACE2 (Zhang et al., 2022). The main part of the RAS, Ang II, is converted by ACE2 into Ang 1-7, which helps widen blood vessels, and it also changes angiotensin I (Ang I) into Ang 1-9 by cutting off one piece (Imai, Kuba, Ohto-Nakanishi, & Penninger, 2010).

In this study, the prevalence of the GG genotype (homozygous wild type) was higher in the case group, comprising 12 people (40%), compared to the control group, which had 10 subjects (33.3%). The occurrence of genotype GA (heterozygous mutant) was higher in the case group, with 9 cases (30%), compared to the control group, which had 6 subjects (10%). The prevalence of the AA (homozygous mutant) genotype was higher in the control group, with 14 individuals (46.7%), compared to the case group, which had 9 individuals (30%). The analysis yielded an odds ratio of 0.750 and a confidence interval of 0.262-2.151, with a p-value of 0.592 ($p > 0.05$). This result is not consistent with the previous study conducted in Dongxiang, China, which found that the frequency of the ACE2 allele 8790A was considerably greater in essential hypertension patients than in controls ($p < 0.0001$) (Yi et al., 2006). The study's findings are in line with earlier research in Anglo-Celtic Australian subjects with hypertension ($n=152$) and normotension ($n=193$), who reported that SNP rs2285666 was not associated with hypertension (Benjafeld, Wang, & Morris, 2004). Another research study in XinYang County, China, provides no evidence that ACE2 G8790A is involved in a hereditary susceptibility to orthostatic hypotension or hypertension (Fan et al., 2009). This study's outcome also agrees with the current meta-analysis, which suggests there may be no connection between the ACE2 G8790A gene polymorphism and the higher risk of essential hypertension in the Chinese population (Pan, 2023).

The response to essential hypertension appeared unaffected by the genetic polymorphism of RAS in our study. The function of RAS in physiological processes explains our findings. Essential hypertension is predominantly attributed to four factors: intravascular volume, autonomic nerve stimulation, the renin-angiotensin system (RAS), and the integrity of blood vessel walls. The underlying causative changes may not be associated with RAS (Sherwood, 2016). Genetic influences on complex traits in Indonesia may be limited or dependent on context, varying among loci, populations, and environmental conditions. This research corresponds with earlier Indonesian investigations about gene-disease correlations, including the rs9939609 FTO gene polymorphism associated with obesity in Cirebon (Pratamawati et al., 2024) and the ACE I/D polymorphism related to essential hypertension in Cirebon (Kuswara et al., 2024). Both studies employ identical geographic and demographic contexts in Cirebon. This study also indicated a non-significant or context-dependent relationship between gene polymorphisms and the complex diseases analyzed in the Cirebon population of West Java.

The ACE2 gene at SNP rs2285666 exhibits variations between ethnicities, distinguished by the presence of Minor Allele Frequency (MAF). MAF denotes the frequency of less common alleles and may fluctuate within a population and between different ethnic groups. In population genetics, MAF denotes the extent of genetic variation within an individual, population, and species. In this study, the frequency of the G allele was 0.49, while the frequency of the A allele was 0.51. According to MAF data from dbSNP NCBI, the Japanese population exhibited a G allele frequency of 0.50 and an A allele frequency of 0.50. In the Vietnamese population, the frequency of the G allele is 0.51, while that of the A allele is 0.49. In the Korean population, the frequencies of the G and A alleles are 0.48 and 0.52, respectively. This research suggests that the minor allele frequency distribution in the Indonesian population closely resembles those of other Asian groups, including Japan, Vietnam, and Korea.

Limitations should be noted. The study's sample size is insufficiently large. To assess the genetic basis of essential hypertension dysregulation, more research is needed to investigate polymorphisms in other gene loci that encode pathways related to the sympathetic nervous system, RAS, vascular system, or kidney system. The researchers were unable to assess the Hardy-Weinberg equilibrium in the control group due to inadequate sample size. Sex-stratified analysis is necessary to ascertain if hemizygous males and heterozygous or homozygous females exhibit distinct genetic risk profiles. Moreover, a haplotype-based methodology may enhance our comprehension of the interactions among various ACE2 variations. More research is recommended with larger groups of people and better statistics to improve our understanding of the link between essential hypertension and ACE2 G8790A.

5. Conclusion

This study did not find an association between ACE2 G8790A and essential hypertension in our sample. Genetic screening for G8790A is not currently indicated in this population. Further research is required on a larger scale to investigate the effects of gene combinations or interactions with other locus genes on essential hypertension. Replication that includes functional assays and a comprehensive investigation of ACE2 polymorphisms is crucial to validate the biological relevance of these findings. This study has several limitations, such as a limited sample size and a single-center design, which may restrict the generalizability of the results.

Conflict of Interest

The authors declare no conflicts of interest for the results.

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Cite this article as:

Husna, N., Nauphar, D., & Pratamawati, T. M. (2025). Angiotensin Converting Enzyme 2 (ACE2) G8790A Gene Polymorphism as a Risk Factor for Essential Hypertension. *GHMJ (Global Health Management Journal)*, 8(2s), 285–292. <https://doi.org/10.35898/ghmj-82s1231>