JAMBI MEDICAL JOURNAL
Jurnal Kedokteran dan Kesehatan
Vol. 14 No 1 May 2026
DOI: 10.22437/jmj.v14i1.43475
Journal homepage: https://online-journal.unja.ac.id/kedokteran
p-Issn : 2339-269x
e-Issn : 2580-6874

Original Article

Genetic Variants Influencing Spironolactone Effectiveness: A Pharmacogenomic Perspective

[1]Danang Prasetyaning Amukti, [2]Ria Indah Pratami, [1]RA Dewinta Sukma Ananda

[1]Department of Pharmacy, Faculty of Health Sciences, Alma Ata University, Yogyakarta, Indonesia
[2]Faculty of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia

E-mail Corresponding: amuktidanang@gmail.com

Article History:

Submit: April 2026
Accepted: Jan 2026

Keyword:

Spironolactone; Pharmacogenomics; Genetic Variants; Gene Expression; Bioinformatics

© 2026 Jambi Medical Journal
Published by Faculty of Medicine and Health Science Universitas Jambi.
This is an open access article under the CC BY-NC-SA license https://creativecommons.org/licenses/by-nc-sa/4.0/

ABSTRACT

Background:
Spironolactone, a mineralocorticoid receptor antagonist, is widely used to treat resistant hypertension, heart failure, and primary aldosteronism. However, significant interindividual variability in therapeutic response suggests a genetic contribution to its effectiveness.

Method:
This study employed a bioinformatics approach using secondary data from PharmGKB, GTEx Portal, and HaploReg v4.2 to identify genetic variants and gene expression profiles potentially influencing spironolactone response.

Result:
Seven variants were identified as associated with spironolactone effectiveness: rs1799752 (ACE), rs3890011 and rs1126742 (CYP4A11), rs1801253 (ADRB1), rs1799983 (NOS3), rs4961 (ADD1), and rs1042713 (ADRB2). Tissue-specific expression analysis showed ACE highly expressed in testis, CYP4A11 in liver, ADRB1 in lung, NOS3 in spleen, ADD1 in tibial artery, and ADRB2 in skin. Functional predictions indicated that missense variants (rs1126742, rs1799983, rs4961) may affect protein structure, while intronic variants (rs1799752, rs3890011) may influence gene regulation.

Conclusion:
These findings suggest that pharmacogenomic profiling may help predict spironolactone response and support the development of personalized treatment strategies. Further clinical validation is required to establish the therapeutic relevance of these variants.

INTRODUCTION

Spironolactone is a potassium-sparing diuretic and mineralocorticoid receptor antagonist widely used in the treatment of resistant hypertension, heart failure with low ejection fraction and primary aldosteronism[1]. By inhibiting the effects of aldosterone in the kidney, spironolactone increases sodium excretion while conserving potassium, thereby reducing fluid retention and improving cardiovascular outcomes[2,3]. However, considerable interindividual variability in response to spironolactone has been observed with some patients

experiencing inadequate blood pressure reduction or increased risk of side effects, such as hyperkalemia and hypotension. This variability suggests underlying genetic influences on drug metabolism, target interactions and sodium homeostasis[4]. Several genetic factors have been implicated in aldosterone signalling, sodium transport, vascular function and drug metabolism, all of which may influence the efficacy of spironolactone. Variations in genes involved in the renin-angiotensin-aldosterone system (RAAS) may affect aldosterone levels and the sensitivity of its receptors, thereby altering the ability of the drug to counteract sodium retention[5,6]. In addition, genes regulating adrenergic signaling, nitric oxide production, and sodium transport mechanisms contribute to differences in blood pressure control and response to diuretics. Understanding these genetic variations is critical to optimizing spironolactone therapy, minimizing side effects, and improving precision medicine approaches in cardiovascular medicine[7].

Recent advances in pharmacogenomics and bioinformatics have facilitated the identification of genetic determinants that may influence the efficacy of spironolactone. Large-scale genomic studies and genome-wide association studies (GWAS) have highlighted key polymorphisms associated with blood pressure regulation, renal function, and drug metabolism, providing valuable insights into individualized treatment strategies[8,9]. In addition, integrating pharmacogenetic data with electronic health records and machine learning models has the potential to refine patient stratification and more accurately predict responders versus nonresponders[10,11]. Incorporating genetic testing into clinical practice may enable dose adjustments and alternative therapy options for patients with a genetic predisposition to poor drug response or increased risk of adverse events. However, despite promising findings, challenges remain in translating pharmacogenomic findings into routine clinical applications, including variability in study populations, lack of standardized genetic testing guidelines, and the need for further validation in different ethnic groups. Addressing these challenges is critical to advancing precision medicine in cardiovascular pharmacotherapy and optimizing spironolactone use based on individual genetic profiles[12,13].

This study aims to explore pharmacogenomic factors that influence the effectiveness of spironolactone, highlighting genetic variants that may contribute to individual differences in drug response. Identifying these genetic determinants may pave the way for personalized treatment strategies, ensuring better therapeutic outcomes for patients with hypertension, heart failure, and aldosterone-related disorders.

METHOD

This study used a secondary data-driven bioinformatics approach to explore genetic variants that influence the efficacy of spironolactone[14]. The two main databases used were PharmGKB and GTEx Portal. Information on genes involved in the mechanism of action of spironolactone, particularly those related to the renin-angiotensin-aldosterone (RAAS) pathway, sodium-potassium homeostasis, and mineralocorticoid receptor (NR3C2) function, was obtained from PharmGKB[8]. From this database, genetic variants (single nucleotide polymorphisms/SNPs) that have been reported to be associated with pharmacological responses to spironolactone or therapeutic agents with similar mechanisms were also curated. In addition, functional analysis of genetic variants was further enhanced using HaploReg v4.2 to evaluate the influence of SNPs on genetic regulatory elements, including prediction of transcription factor binding, evolutionary conservation, and correlation with epigenetic marks such as histone modifications and DNA methylation. Allele frequency data from global populations were obtained from the 1000 Genomes Project, while predictions of the functional impact of SNPs were analyzed through the dbSNP database. Next, gene

expression analysis was performed using GTEx Portal to evaluate the tissue expression of candidate genes, focusing on tissues that are the main targets of spironolactone action. The mRNA expression data were used to assess the biological potential of these genes in influencing pharmacological responses. These findings are expected to be the basis for the development of precision medicine strategies that consider individual genetic profiles.

RESULT AND DISCUSSION

Identification of Genetic Variants Associated with Spironolactone Effectiveness

Data exploration results through February 25 from PharmGKB revealed seven genetic variants that could potentially affect the effectiveness of spironolactone in various clinical conditions. Each variant was categorized as an efficacy group and supported by an evidence level of 3, indicating a significant initial association but still open to further validation in a broader population. One notable finding was the rs1799752 variant in the *ACE* gene , which has been associated with response to spironolactone therapy in patients with heart failure. This gene is an integral part of the renin-angiotensin system, and its variations are thought to affect the activity of angiotensin-converting enzyme, which in turn impacts the effectiveness of aldosterone inhibition. Interestingly, two variants in the *CYP4A11* gene rs3890011 and rs1126742 were found to be associated with spironolactone response in hypertensive patients. These genes are involved in arachidonic acid metabolism that contributes to blood pressure regulation, so variations in them have the potential to affect spironolactone metabolism and its antihypertensive effects.

In addition, the role of the adrenergic system is also reflected by the identification of variants rs1801253 and rs1042713 in the *ADRB1* and *ADRB2* genes, respectively , both of which are associated with the effectiveness of spironolactone in heart failure. These variations may modulate the response to sympathetic stress and affect blood pressure regulation. The variant rs1799983 in the *NOS3* gene, encoding endothelial nitric oxide synthase, was found to be associated with the effectiveness of spironolactone in heart failure, strengthening the link between the vasodilatory pathway and the therapeutic action of spironolactone. Outside the cardiovascular context, the variant rs4961 in the *ADD1* gene, which affects renal sodium transport, has been shown to potentially influence the response to spironolactone in patients with liver cirrhosis. Overall, these findings highlight the complex but promising pharmacogenetic landscape in the use of spironolactone. The identification of these variants opens up opportunities for more precision medicine strategies, targeting therapy to patients most likely to benefit and minimizing the risk of side effects

Table 1. Genetic Variants Associated with Spironolactone Effectiveness

Variants	Gene	Drugs	Phenotype Categories	Phenotype	Evidence Level	PharmGKB ID
rs1799752	*ACE*	Spironolactone	Efficacy	Heart Failure	3	982036328
rs3890011	*CYP4A11*	Spironolactone	Efficacy	Hypertension	3	1450821128
rs1126742	*CYP4A11*	Spironolactone	Efficacy	Hypertension	3	1450821121
rs1801253	*ADRB1*	Spironolactone	Efficacy	Heart Failure	3	1447960443
rs1799983	*NOS3*	Spironolactone	Efficacy	Heart Failure	3	1444700983
rs4961	*ADD1*	Spironolactone	Efficacy	Liver Cirrhosis	3	981202806
rs1042713	*ADRB2*	Spironolactone	Efficacy	Heart Failure	3	1447960179

Analysis of Genetic Variation and Its Potential Influence on Spironolactone Response

The results of the exploration using haploreg v4.2 can be seen in Table 2, which presents seven genetic variations (SNPs) that may play a role in determining the response to spironolactone therapy. Variations rs1799752 and rs3890011 are intronic variants whose alternative allele frequencies vary significantly between populations, with rs3890011 showing a high frequency (0.77) in European populations. Four missense variants (rs1126742, rs1801253, rs1799983, and rs4961) are of particular interest because of their potential to alter protein structure, where rs1799983 and rs4961 are located in regions of the genome that experience strong selection pressure according to both the GERP and SiPhy methods. Variant rs1042713, although it has no known functional annotation, shows a different allele frequency distribution between populations, with the highest frequency (0.54) in Asian populations. These differences in allele frequencies between populations may also explain the variation in clinical response to spironolactone observed in different ethnic groups. These findings highlight the importance of considering pharmacogenomic factors in the use of spironolactone, especially for patients with specific genetic profiles or who show atypical responses to therapy. However, the clinical interpretation of these variants requires further study to validate their functional significance and association with spironolactone therapy outcomes.

Table 2. Genetic Variations Associated with Response to Spironolactone Therapy

Variants	Reference	Alternate	1000 Genomes Phase 1 Frequencies				Sequence constraint		dbSNP functional annotation
			AFR	AMR	ASN	EUR	by GERP	by SiPhy	
rs1799752	T	TATACAGTCACTTTTTTTTTTTTTTT GAGACGGAGTCTCGCTCTGTCGCCC	0	0	0	0	No	No	intronic
rs3890011	G	C	0.33	0.7	0.49	0.77	No	No	intronic
rs1126742	A	G	0.23	0.13	0.2	0.14	Yes	No	missense
rs1801253	G	C	0.6	0.79	0.79	0.66	No	Yes	missense
rs1799983	T	G	0.94	0.76	0.88	0.68	Yes	Yes	missense
rs4961	G	T	0.05	0.18	0.5	0.22	Yes	Yes	missense
rs1042713	G	A	0.53	0.47	0.54	0.38	No	Yes	none

Analysis of Gene Expression and Its Potential Influence on Spironolactone Response

The *ACE* (Angiotensin-Converting Enzyme) gene shows the highest expression in the testis , but is also widely expressed in other tissues such as the lungs, kidneys, and blood vessels. In the renin-angiotensin-aldosterone system (RAAS), *ACE* plays an important role in converting angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates aldosterone secretion. As a mineralocorticoid receptor antagonist, spironolactone works by inhibiting the effects of aldosterone, so high *ACE* expression in the testis may indicate local regulation of the RAAS in this tissue[15,16]

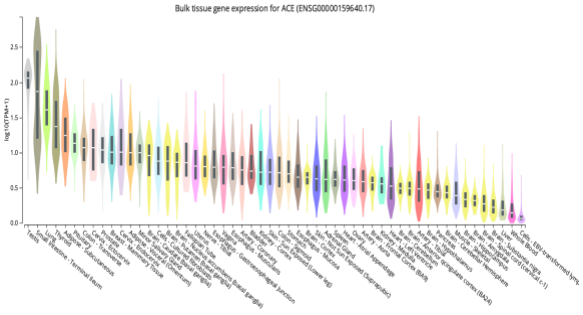

Figure 1. *ACE* gene expression in all body tissues.

The *CYP4A11* gene, which shows the highest expression in the liver, plays an important role in lipid metabolism as well as drug biotransformation. In the context of

pharmacokinetics, spironolactone undergoes extensive metabolism in the liver, mainly via the enzymes *CYP3A4* and *CYP2C8*, producing active metabolites such as canrenone, 7α-thiomethyl-spironolactone, and 6β-hydroxy-spironolactone that contribute to its pharmacological effects as a mineralocorticoid antagonist. Its high expression in the liver indicates its possible contribution to the secondary metabolic pathways of this drug[17,18].

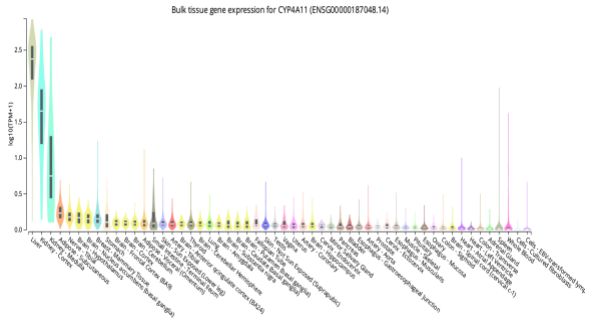

Figure 2. Expression of the *CYP4A11* gene in all body tissues.

The *ADRB1* (Adrenergic Beta-1 Receptor) gene shows the highest expression in the lungs, indicating its important role in the regulation of adrenergic responses in this tissue. As part of the β-adrenergic receptors, *ADRB1* functions in regulating the contraction and relaxation of airway smooth muscle and plays a role in pulmonary cardiovascular responses including blood pressure regulation in the pulmonary circulation. *ADRB1* activation by catecholamines such as adrenaline and noradrenaline can affect bronchodilation and pulmonary blood pressure homeostasis[19].

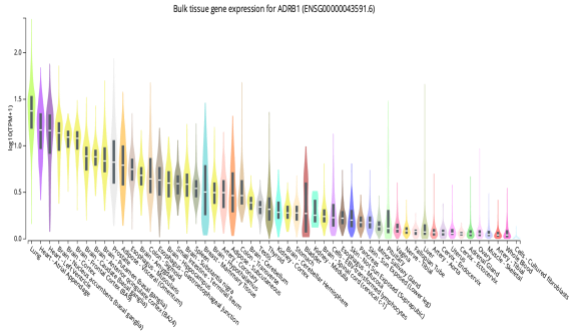

Figure 3. *ADRB1* gene expression in all body tissues.

The *NOS3* (Nitric Oxide Synthase 3) gene shows the highest expression in the spleen , but is also expressed in blood vessels, heart, and kidneys. This enzyme is responsible for producing nitric oxide (NO), an important signaling molecule that plays a role in vasodilation, blood pressure regulation, and endothelial function[20,21].

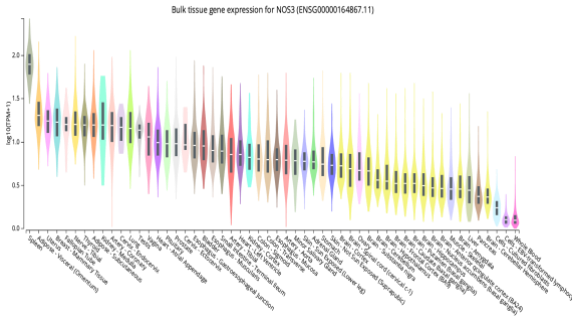

Figure 4. *NOS3* gene expression in all body tissues.

Gene ***ADD1*** **(Adducin 1)** shows the highest expression in **tibial artery**, as well as being expressed in the kidney and other vascular tissues. Adducin proteins play a role in stabilizing the cell cytoskeleton, particularly in regulating cell membrane structure and ion transport. *ADD1* can affect effectiveness of spironolactone through regulation of ion transport in the blood vessels, which affects peripheral resistance and blood pressure. In patients with *ADD1* genetic variations, the response to spironolactone may differ due to differences in sodium homeostasis[22].

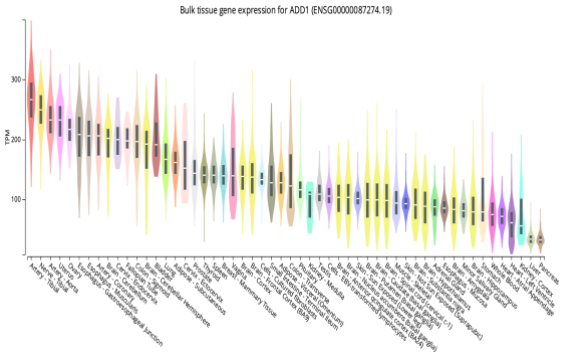

Figure 5. *ADD1* gene expression in all body tissues.

Gene *ADRB2* (Adrenoceptor Beta 2) shows the highest expression in skin, as well as being expressed in the lungs, skeletal muscle, and vascular tissues. These β2-adrenergic receptors play important roles in a variety of

physiological processes that may interact with the mechanism of action of spironolactone. Expression in the skin suggests a potential local effect of spironolactone on fluid and electrolyte regulation in skin tissues[23].

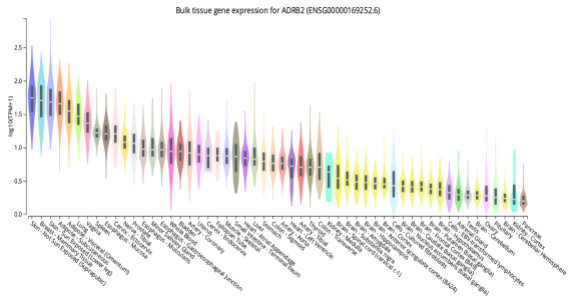

Figure 6. *ADRB2* gene expression in all body tissues.

The highest expression of *ACE* (Angiotensin-Converting Enzyme) in the testes suggests that this enzyme has functions that are not only limited to the renin-angiotensin system, but also plays a role in spermatogenesis and male fertility. Testis-specific isoforms of *ACE* have been shown to contribute to sperm maturation and regulation of sperm motility. A study published in Nature Medicine showed that the dipeptidase activity of testicular *ACE* is critical for male fertility, where mutations or *ACE* deficiencies can disrupt the sperm maturation process and reduce fertility[24]. In the context of the relationship with spironolactone, this drug has antiandrogenic effects, meaning it can reduce testosterone levels or interfere with androgen action in target tissues, including the testes. Long-term or high-dose use of spironolactone has been associated with side effects such as gynecomastia and decreased libido that can potentially affect fertility. Although there has been no direct research linking high *ACE* expression in the testes with the effectiveness of spironolactone, it is known that disruption of the androgen hormone balance due to spironolactone can impact testicular function including *ACE* expression and activity[24].

Pharmacogenomic studies have shown that Insertion/Deletion (I/D) polymorphisms in the *ACE* gene (rs1799752) are known to affect plasma *ACE* levels which are implicated in aldosterone regulation. Individuals with the DD (Deletion/Deletion) genotype have higher *ACE* levels, which increase the conversion of angiotensin I to angiotensin II[25]. This leads to increased aldosterone secretion, so individuals with the DD genotype tend to experience relative hyperaldosteronism and show a better response to spironolactone. Conversely, individuals with the II (Insertion/Insertion) genotype have lower *ACE* levels so that the inhibitory effect of aldosterone by spironolactone may be more limited. In addition, *ACE* also plays a role in cardiovascular remodeling, where the DD genotype is associated with more severe myocardial fibrosis and increased vascular stiffness, which are major factors in heart failure and resistant hypertension. In this context, patients with the DD genotype may benefit more from spironolactone therapy than individuals with genotype II, who have lower *ACE* levels and may experience a more minimal therapeutic effect. Thus, understanding *ACE* genetic variants may help personalize spironolactone therapy, especially in patients with resistant hypertension or heart failure that relies on aldosterone regulation[26].

CYP4A11 gene is part of the cytochrome P450 family that plays a role in fatty acid metabolism and blood pressure regulation through the production of 20-hydroxy-eicosatetraenoic acid (20-HETE) a metabolite that regulates sodium excretion and renal blood flow. The rs3890011 and rs1126742 polymorphisms in the CYP4A11 gene have been associated with changes in enzyme activity that affect blood pressure and response to antihypertensive therapy, including spironolactone[27,28]. The rs3890011 variant can cause decreased *CYP4A11* activity leading to impaired 20-HETE production and excess sodium retention, thereby increasing blood pressure. Spironolactone, which works as an aldosterone antagonist to increase sodium excretion, may be more effective, making patients with this variant more responsive to spironolactone therapy. In addition, the

rs1126742 (T8590C) polymorphism is also known to affect the activity of the *CYP4A11* enzyme, where the C variant (rs1126742 mutation) is associated with decreased production of 20-HETE which can cause essential hypertension due to higher sodium retention. In patients with this variant, spironolactone can provide a more optimal therapeutic effect in reducing blood pressure and preventing excessive fluid retention. Therefore, individuals with the rs3890011 and rs1126742 polymorphisms that cause decreased *CYP4A11* activity have the potential to have a better response to spironolactone compared to individuals without this variant. The *ADRB1* gene shows the highest expression in the lungs, indicating its important role in regulating adrenergic responses in this tissue[29,30]. As part of the β-adrenergic receptor, *ADRB1* functions in regulating contraction and relaxation of airway smooth muscle and plays a role in pulmonary cardiovascular responses including regulation of blood pressure in the pulmonary circulation. *ADRB1* activation by catecholamines such as adrenaline and noradrenaline can affect bronchodilation and pulmonary blood pressure homeostasis. In the context of pharmacology, spironolactone as a mineralocorticoid antagonist can affect the renin-angiotensin-aldosterone system (RAAS) which interacts with the adrenergic system[31]. Several studies have shown that spironolactone can modulate the sensitivity of adrenergic receptors, including *ADRB1* which plays a role in cardiac contractility and vascular resistance. This effect may have an impact on conditions such as pulmonary hypertension, where aldosterone antagonism by spironolactone has the potential to reduce vascular remodeling and increase adrenergic responses[32].

The *ADRB1* gene encodes a β1-adrenergic receptor that plays a role in the regulation of blood pressure and cardiovascular function. The rs1801253 (Gly389Arg) polymorphism causes a change in the amino acid Glycine (Gly) to Arginine (Arg), which increases the response to catecholamine stimulation. Individuals with the Arg389 variant have higher β1 receptor activity, which can lead to increased blood pressure and risk of heart failure[33,34]. Spironolactone, as an aldosterone antagonist, may help reduce the higher activation of the renin-angiotensin-aldosterone system (RAAS) in individuals with this variant, so Arg389 patients may potentially benefit more from spironolactone therapy in lowering blood pressure and reducing cardiac workload. The *NOS3* (Nitric Oxide Synthase 3) gene plays a role in the production of nitric oxide (NO), which is an important vasodilator in regulating blood pressure. The rs1799983 (Glu298Asp) polymorphism causes the amino acid substitution of Glutamate (Glu) to Aspartate (Asp), which is associated with decreased NO production and increased risk of hypertension and endothelial dysfunction. Since spironolactone can increase NO availability by reducing oxidative stress and vascular resistance, patients with the Asp298 variant who have lower NO production may benefit more from spironolactone therapy in reducing blood pressure and improving vascular function[35].

The *ADD1* (Adducin 1) gene plays a role in regulating sodium transport in the kidneys which affects sodium balance and blood pressure. The rs4961 (Gly460Trp) polymorphism causes the substitution of Glycine (Gly) to Tryptophan (Trp) which is associated with increased sodium reabsorption in the kidneys, which can cause essential hypertension[34,36]. Spironolactone works by inhibiting the effect of aldosterone to increase sodium excretion, so individuals with the Trp460 variant who tend to experience hypertension due to excess sodium retention, can show a better response to spironolactone than individuals without this mutation. The ADRB2 (Adrenergic Beta-2 Receptor) gene encodes a β2-adrenergic receptor that plays a role in vasodilation and blood pressure regulation. The rs1042713 (Arg16Gly) polymorphism causes the substitution of Arginine (Arg) to Glycine (Gly) which can affect the sensitivity of the receptor to

catecholamine stimulation. Individuals with the Arg16 variant have lower β2 receptor activity, which may result in more dominant vasoconstriction, increased blood pressure, and worsened vascular dysfunction. Spironolactone may help reduce the vasoconstrictive effects of low β2 activity, so patients with the Arg16 variant may benefit more from spironolactone therapy in reducing blood pressure and improving endothelial function[37].

CONCLUSION

Based on the bioinformatics analysis conducted, this study successfully identified seven genetic variants (rs1799752, rs3890011, rs1126742, rs1801253, rs1799983, rs4961, and rs1042713) that potentially affect the effectiveness of spironolactone through various mechanisms, including drug metabolism, aldosterone signaling, and blood pressure regulation. The tissue-specific expression patterns of related genes (*ACE, CYP4A11, ADRB1, NOS3, ADD1*, and *ADRB2*) indicate that the interaction of spironolactone with the body's physiological systems is complex and depends on individual genetic characteristics. These findings reinforce the importance of a pharmacogenomic approach in the use of spironolactone, especially to predict therapeutic response and minimize side effects. Genetic variants involved in drug metabolism (*CYP4A11*) and blood pressure regulation (*ACE, ADRB1, NOS3*) may be potential markers for patient stratification. However, further clinical validation is needed to confirm the functional significance of these variants in more diverse populations.

REFERENCES

1. *Manolis AA, Manolis TA, Melita H, Manolis AS. Spotlight on Spironolactone Oral Suspension for the Treatment of Heart Failure: Focus on Patient Selection and Perspectives. Vasc Health Risk Manag. 2019 Dec 30;15:571-579. doi: https://doi.org/10.2147/VHRM.S210150 . PMID: 31920323; PMCID: PMC6941679.*
2. *Banerjee S, Navasundi GB, Vora A, Arneja J, Sharma K, Jaswal A, Kannan K, Kumar P, Bharti BB, Singh UN, Garg R, Aila P, Zalte N, Sugumaran A. Fixed-dose Combination of Torsemide and Mineralocorticoid Receptor Antagonists. J Assoc Physicians India. 2024 Sep;72(9S):40-42. doi: https://doi.org/10.59556/japi.72.0678 . PMID: 39291574.*
3. *Funder JW. Spironolactone in cardiovascular disease: an expanding universe? F1000Res. 2017 Sep 22;6:1738. doi: https://doi.org/10.12688/f1000research.11887.1 . PMID: 29034087; PMCID: PMC5615771.*
4. *Lainscak M, Pelliccia F, Rosano G, Vitale C, Schiariti M, Greco C, Speziale G, Gaudio C. Safety profile of mineralocorticoid receptor antagonists: Spironolactone and eplerenone. Int J Cardiol. 2015 Dec 1;200:25-9. doi: https://doi.org/10.1016/j.ijcard.2015.05.127 . Epub 2015 May 21. PMID: 26404748.*
5. *Ghazi L, Drawz P. Advances in understanding the renin-angiotensin-aldosterone system (RAAS) in blood pressure control and recent pivotal trials of RAAS blockade in heart failure and diabetic nephropathy. F1000Res. 2017 Mar 21;6:F1000 Faculty Rev-297. doi: https://doi.org/10.12688/f1000research.9692.1 . PMID: 28413612; PMCID: PMC5365219.*
6. *Abdel Ghafar MT. An overview of the classical and tissue-derived renin-angiotensin-aldosterone system and its genetic polymorphisms in essential hypertension. Steroids. 2020 Nov;163:108701. doi: https://doi.org/10.1016/j.steroids.2020.108701 . Epub 2020 Jul 24. PMID: 32717198.*
7. *Mirabito Colafella KM, Bovée DM, Danser AHJ. The renin-angiotensin-aldosterone system and its therapeutic targets. Exp Eye Res. 2019 Sep;186:107680. doi: https://doi.org/10.1016/j.exer.2019.05.020 . Epub 2019 May 23. PMID: 31129252.*

8. *Amukti DP, Wazni AR, Irham LM, Sulistyani N, Ma'ruf M, Adikusuma W, Sarasmita MA, Khairi S, Purwanto BD, Suyatmi S, Siswanto LM. Identifying pathogenic variants associated with Alzeimer by integrating genomic databases and bioinformatics approaches. InE3S Web of Conferences 2024 (Vol. 501, p. 01021). EDP Sciences.*
9. *Humolungo DT, Anjani R, Irham LM, Sulistyani N, Ma'ruf M, Amukti DP, Adikusuma W, Sarasmita MA, Khairi S, Purwanto BD, Suyatmi S. Identification of pathogenic gene variants in carpal tunnel syndrome using bioinformatics approaches. InE3S Web of Conferences 2024 (Vol. 501, p. 01022). EDP Sciences.*
10. *Irham LM, Amukti DP, Adikusuma W, Singh D, Chong R, Pranata S, et al. Trends in drug repurposing for chronic hepatitis-B infection:bibliometric-basedapproach1990-2024. In: BIO Web of Conferences. EDP Sciences; 2025.*
11. *Made I, Wijaya H, Fahrian Hipmi A, Nur S, Abas R, Amukti DP, et al. POTENSI VARIASI GEN FGL1 DALAM PENINGKATAN RISIKO EFEK SAMPING PADA HATI AKIBAT PENGGUNAAN NIFEDIPIN PADA PASIEN HIPERTENSI GESTASIONAL. Jurnal Ilmu Farmasi dan Farmasi Klinik (JIFFK) [Internet]. 2024;21(2):269–76. Available from: https://www.ebi.ac.uk/gwas/*
12. *Irham LM, Amukti DP, Adikusuma W, Singh D, Chong R, Basyuni M, et al. Applied of bioinformatics in drug discovery and drug development: Bioinformatic analysis 1996-2024. Zubaidah S, Saifuddin MF, de Carvalho GS, Sugahara T, Lestari SR, Ziarati P, et al., editors. BIO Web Conf [Internet]. 2024 Jan 9;148:01003. Available from: https://www.bio-conferences.org/10.1051/bioconf/202414801003*
13. *Amukti DP, Irham LM, Surono S, Adikusuma W, Chong R, El Khair R, et al. Genomic variants and epidemiology of atherosclerosis – worldwide correlation analysis and utilization of atherosclerosis gene variants for identification of drug target candidates with bioinformatics approach. Bulgarian Cardiology [Internet]. 2024 Dec 31;30(4):108–20. Available from: https://journal.bgcardio.org/article/145391/*
14. *Gumelar G, Ulfa MM, Amukti DP, Irham LM, Yuliani S, Adikusuma W, et al. Harnessing Genomic and Bioinformatic Data to Broaden Understanding of Leukaemia Across Continents. Scripta Medica (Banja Luka). 2024 Nov 1;55(6):717–25.*
15. *Cadegiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARS-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS). Med Hypotheses. 2020 Oct;143:110112. doi: https://doi.org/10.1016/j.mehy.2020.110112 . Epub 2020 Jul 16. PMID: 32721806; PMCID: PMC7363620.*
16. *Stoll D, Yokota R, Sanches Aragão D, Casarini DE. Both aldosterone and spironolactone can modulate the intracellular ACE/ANG II/AT1 and ACE2/ANG (1-7)/MAS receptor axes in human mesangial cells. Physiol Rep. 2019 Jun;7(11):e14105. doi: 10.14814/phy2.14105. PMID: 31165585; PMCID: PMC6548847.*
17. *Dahmana N, Gabriel D, Gurny R, Kalia YN. Development and validation of a fast and sensitive UHPLC-ESI-MS method for the simultaneous quantification of spironolactone and its metabolites in ocular tissues. Biomed Chromatogr. 2018 Oct;32(10):e4287. doi: https://doi.org/10.1002/bmc.4287 . Epub 2018 Jun 19. PMID: 29767448.*
18. *Schiffer L, Müller AR, Hobler A, Brixius-Anderko S, Zapp J, Hannemann F, Bernhardt R. Biotransformation of the mineralocorticoid receptor antagonists spironolactone and canrenone by human CYP11B1 and CYP11B2: Characterization of the products and their influence on mineralocorticoid receptor transactivation. J Steroid Biochem Mol Biol. 2016 Oct;163:68-76. doi: https://doi.org/10.1016/j.jsbmb.2016.04.004 . Epub 2016 Apr 25. PMID: 27125452.*
19. *Danahay H, Fox R, Lilley S, Charlton H, Adley K, Christie L, Ansari E, Ehre C, Flen A, Tuvim MJ, Dickey BF, Williams C, Beaudoin S, Collingwood SP, Gosling M. Potentiating TMEM16A does not stimulate airway mucus secretion or bronchial and pulmonary arterial smooth muscle contraction. FASEB Bioadv. 2020 Jul 1;2(8):464-477. doi: https://doi.org/10.1096/fba.2020-00035 . PMID: 32821878; PMCID: PMC7429354.*

20. *Zou D, Li Z, Lv F, Yang Y, Yang C, Song J, Chen Y, Jin Z, Zhou J, Jiang Y, Ma Y, Jing Z, Tang Y, Zhang Y. Pan-Cancer Analysis of NOS3 Identifies Its Expression and Clinical Relevance in Gastric Cancer. Front Oncol. 2021 Mar 4;11:592761. doi: https://doi.org/10.3389/fonc.2021.592761 . PMID: 33747912; PMCID: PMC7969995.*
21. *Luizon MR, Pereira DA, Tanus-Santos JE. Pharmacogenetic relevance of endothelial nitric oxide synthase polymorphisms and gene interactions. Pharmacogenomics. 2018 Dec;19(18):1423-1435. doi: https://doi.org/10.2217/pgs-2018-0098 . Epub 2018 Nov 6. PMID: 30398085.*
22. *Lechuga S, Amin PH, Wolen AR, Ivanov AI. Adducins inhibit lung cancer cell migration through mechanisms involving regulation of cell-matrix adhesion and cadherin-11 expression. Biochim Biophys Acta Mol Cell Res. 2019 Mar;1866(3):395-408. doi: https://doi.org/10.1016/j.bbamcr.2018.10.001 . Epub 2018 Oct 2. PMID: 30290240; PMCID: PMC6311435.*
23. *Cho HW, Shin S, Song KD, Park JW, Choi JY, Lee HK, Cho BW. Molecular Characterization and Expression Analysis of Adrenergic Receptor Beta 2 (ADRB2) Gene before and after Exercise in the Horse. Asian-Australas J Anim Sci. 2015 May;28(5):686-90. doi: https://doi.org/10.5713/ajas.14.0573 . PMID: 25924960; PMCID: PMC4412999.*
24. *Fuchs S, Frenzel K, Hubert C, Lyng R, Muller L, Michaud A, Xiao HD, Adams JW, Capecchi MR, Corvol P, Shur BD, Bernstein KE. Male fertility is dependent on dipeptidase activity of testis ACE. Nat Med. 2005 Nov;11(11):1140-2; author reply 1142-3. doi: https://doi.org/10.1038/nm1105-1140 . PMID: 16270063.*
25. *Ghorbani E, Mohammadi M, Malakouti SK, Mohammadi-Kangarani H, Abdollahi E, Torab M, Rahimi-Moghaddam P. Association of ACE Gene Insertion/Deletion Polymorphism with Suicidal Attempt in an Iranian Population. Biochem Genet. 2021 Feb;59(1):31-41. doi: https://doi.org/10.1007/s10528-020-09986- 7. Epub 2020 Jul 27. PMID: 32720141.*
26. *Wang Y, Lu H, Chen Y, Luo Y. The association of angiotensin-converting enzyme gene insertion/deletion polymorphisms with adaptation to high altitude: A meta-analysis. J Renin Angiotensin Aldosterone Syst. 2016 Mar 23;17(1):1470320315627410. doi: https://doi.org/10.1177/1470320315627410 . PMID: 27009284; PMCID: PMC5843938.*
27. *Oliveira-Paula GH, Pereira SC, Tanus-Santos JE, Lacchini R. Pharmacogenomics And Hypertension: Current Insights. Pharmgenomics Pers Med. 2019 Nov 22;12:341-359. doi: https://doi.org/10.2147/PGPM.S230201 . PMID: 31819590; PMCID: PMC6878918.*
28. *Luizon MR, Pereira DA, Sandrim VC. Pharmacogenomics of Hypertension and Preeclampsia: Focus on Gene-Gene Interactions. Front Pharmacol. 2018 Feb 28;9:168. doi: 10.3389/fphar.2018.00168. PMID: 29541029; PMCID: PMC5835759.*
29. *Luo G, Ai Y, Zhu T, Li J, Ren Z. FTO promoted adipocyte differentiation by regulating ADRB1 gene through m6A modification in Hycole rabbits. Anim Biotechnol. 2023 Dec;34(7):2565-2570. doi: https://doi.org/10.1080/10495398.2022.2105229 . Epub 2022 Jul 29. PMID: 35904284.*
30. *Muslimova E, Rebrova T, Kondratieva D, Korepanov V, Sonduev E, Kozlov B, Afanasiev S. Expression of the β1-adrenergic receptor (ADRB1) gene in the myocardium and β-adrenergic reactivity of the body in patients with a history of myocardium infraction. Gene. 2022 Nov 30;844:146820. doi: https://doi.org/10.1016/j.gene.2022.146820 . Epub 2022 Aug 17. PMID: 35987510.*
31. *Cadegiani FA, Goren A, Wambier CG. Spironolactone may provide protection from SARS-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS). Med Hypotheses. 2020 Oct;143:110112. doi: https://doi.org/10.1016/j.mehy.2020.110112 . Epub 2020 Jul 16. PMID: 32721806; PMCID: PMC7363620.*
32. *Akhtar H, Al Sudani H, Hussein M, Farhan MUN, Elkholy K. Effects of Renin-Angiotensin-Aldosterone System Inhibition on Left Ventricular Hypertrophy, Diastolic Function, and Functional Status in Patients With Hypertrophic Cardiomyopathy: A Systematic Review. Cureus. 2022 Jul 7;14(7):e26642. doi: 10.7759/cureus.26642. PMID: 35949750; PMCID: PMC9356743.*

33. *Anthony EG, Richard E, Lipkowitz MS, Bhatnagar V. Association of the ADRB2 (rs2053044) polymorphism and angiotensin-converting enzyme-inhibitor blood pressure response in the African American Study of Kidney Disease and Hypertension. Pharmacogenet Genomics. 2015 Sep;25(9):444-9. doi: https://doi.org/10.1097/FPC.0000000000000154 . PMID: 26111150.*
34. *Kelley EF, Snyder EM, Johnson BD. Influence of Beta-1 Adrenergic Receptor Genotype on Cardiovascular Response to Exercise in Healthy Subjects. Cardiol Res. 2018 Dec;9(6):343-349. doi: https://doi.org/10.14740/cr785 . Epub 2018 Dec 7. PMID: 30627284; PMCID: PMC6306116.*
35. *Shahid SU; Shabana; Rehman A. Association Patterns of Endothelial Nitric Oxide Synthase Gene (NOS3) Variant Glu298Asp with Blood Pressure and Serum Lipid Levels in Subjects with Coronary Artery Disease from Pakistan. Ann Hum Genet. 2017 Jul;81(4):129-134. doi: https://doi.org/10.1111/ahg.12192 . PMID: 28620990.*
36. *Sydorchuk L, Lytvyn B, Sydorchuk A, Yarynych Y, Daruvuri SP, Semenenko S, Hoshovska A, Sydorchuk R, Biryuk I. Alpha-adducin 1 (rs4961) gene and its expression associated with sodium sensitivity in hypertensive patients: a cohort study in the western Ukrainian population. Endocr Regul. 2024 Oct 1;58(1):195-205. doi: https://doi.org/10.2478/enr-2024-0023 . PMID: 39352780.*
37. *Dmytriiev K, Mostovoy Y, Slepchenko N, Smereka Y. Clinical course of COPD in patients with Arg16Gly (rs1042713) polymorphism of ADRB2 gene. Monaldi Arch Chest Dis. 2022 Sep 13;93(2). doi: https://doi.org/10.4081/monaldi.2022.2314 . PMID: 36111412.*