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## PERSONALIZING AMLODIPINE THERAPY IN HYPERTENSION THE ROLE OF GENETIC VARIANTS AND POPULATION-SPECIFIC RESPONSES

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## ПЕРСОНАЛИЗИРАНЕ НА ТЕРАПИЯТА С АМЛОДИПИН ПРИ ХИПЕРТОНИЯ – РОЛЯТА НА ГЕНЕТИЧНИТЕ ВАРИАНТИ И СПЕЦИФИЧНИТЕ РЕАКЦИИ НА НАСЕЛЕНИЕТО

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### Abstract.

**Introduction:** Amlodipine is a long-acting dihydropyridine calcium channel blocker used in hypertension management. Despite its widespread use, therapeutic response varies significantly among individuals, influenced by genetic, environmental, and physiological factors. Pharmacogenomics, which studies genetic variation affecting drug responses, has identified specific genetic variants associated with amlodipine metabolism and efficacy. Genes such as *CYP3A4*, *RYR3*, *CACNA1C*, and *CACNA1D* are known to play a role in amlodipine's pharmacokinetics and pharmacodynamics. This review examines these genetic variants and their impact on amlodipine efficacy, with a focus on population-specific responses. **Material and methods:** This study utilized publicly available pharmacogenomic data from the PharmGKB and GTEx Portal to identify genetic variants associated with amlodipine efficacy. Genetic variants from *CYP3A4*, *RYR3*, *CACNA1C*, and *CACNA1D* were selected based on their association with amlodipine response. Population-specific variations were also analyzed to assess differences in therapeutic outcomes across diverse biogeographical groups. **Results:** Seven single nucleotide polymorphisms (SNPs) from four genes were identified: *CYP3A4* (rs2246709, rs2740574), *RYR3* (rs877087), *CACNA1C* (rs2239050, rs2239128), and *CACNA1D* (rs312481). SNPs such as rs2246709 in *CYP3A4* and rs877087 in *RYR3* were linked to enhanced amlodipine efficacy in certain populations, while rs2740574 showed greater response in women. Variants like rs2239050 and rs312481 influenced amlodipine response in Central/South Asian and European populations. **Conclusion:** Genetic variants, including *CYP3A4* (rs2246709, rs2740574), *RYR3* (rs877087), *CACNA1C* (rs2239050, rs2239128), and *CACNA1D* (rs312481), significantly influence amlodipine efficacy in hypertensive patients. These findings underscore the importance of genetic factors in personalizing hypertension treatment and optimizing drug efficacy across diverse populations. However, further clinical validation and mechanistic studies are necessary to confirm the therapeutic implications of these genetic associations. Understanding the distribution of these variants across populations may aid in tailoring amlodipine therapy based on ethnic and geographical factors, ensuring a more precise and effective treatment approach.

### Key words:

hypertension, amlodipine, pharmacogenomics, genetic variants, *CYP3A4*, *RYR3*, *CACNA1C*, *CACNA1D*, single nucleotide polymorphisms, drug efficacy, population-specific response, calcium channel blocker, precision medicine

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### Резюме.

**Въведение:** Амлодипин е дългодействащ дихидропиридинов блокатор на калциевите канали, използван за лечение на хипертония. Въпреки широката му употреба терапевтичният отговор варира значително при отделните индивиди, тъй като се влияе от генетични, екологични и физиологични фактори. Фармакогеномиката, която изучава генетичните вариации, влияещи върху лекарствените реакции, е идентифицирала специфични генетични варианти, свързани с метаболизма и ефикасността на амлодипин. Известно е, че гени като *CYP3A4*, *RYR3*, *CACNA1C* и *CACNA1D* играят роля във фармакокинетиката и фармакодинамиката на амлодипин. В този материал се разглеждат тези генетични варианти и тяхното въздействие върху ефикасността на амлодипин, като се акцентира върху специфичните за популацията реакции. **Материал и методи:** В това проучване бяха

използвани публично достъпни фармакогеномни данни от порталите PharmGKB и GTEx, за да се идентифицират генетични варианти, свързани с ефикасността на амлодипин. Специфичните за популацията вариации също бяха анализирани, за да се оценят разликите в терапевтичните резултати в различните биогеографски групи. **Резултати:** Бяха установени седем единични нуклеотидни полиморфизма (SNP) от четири гена: *CYP3A4* (rs2246709, rs2740574), *RYR3* (rs877087), *CACNA1C* (rs2239050, rs2239128) и *CACNA1D* (rs312481). SNP като rs2246709 в *CYP3A4* и rs877087 в *RYR3* са свързани с повишена ефикасност на амлодипин в определени популации, докато rs2740574 показва по-голям отговор при жените. Варианти като rs2239050 и rs312481 са повлияли на отговора на амлодипин при популации от Централна/Южна Азия и Европа. **Заключение:** Генетичните варианти, включително *CYP3A4* (rs2246709, rs2740574), *RYR3* (rs877087), *CACNA1C* (rs2239050, rs2239128) и *CACNA1D* (rs312481), оказват значително влияние върху ефикасността на амлодипин при пациенти с хипертония. Тези констатации подчертават значението на генетичните фактори за персонализиране на терапията при хипертония и за оптимизиране на ефикасността на лекарствата при различни популации. Въпреки това са необходими допълнителни клинични валидации и механизтични проучвания, за да се потвърдят терапевтичните последици от тези генетични асоциации. Разбирането на разпределението на тези варианти сред популациите може да помогне за адаптиране на терапията с амлодипин въз основа на етнически и географски фактори, като се гарантира по-прецизен и ефективен подход към лечението.

**Ключови думи:** хипертония, амлодипин, фармакогеномика, генетични варианти, *CYP3A4*, *RYR3*, *CACNA1C*, *CACNA1D*, единични нуклеотидни полиморфизми, лекарствена ефикасност, специфичен за популацията отговор, блокер на калциевите канали, прецизна медицина

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## INTRODUCTION

Hypertension is a leading global health concern, affecting over 1.3 billion people worldwide and contributing significantly to cardiovascular diseases, stroke, and renal failure [1, 2]. Effective management of hypertension is critical to reducing morbidity and mortality rates [3]. Among the various antihypertensive agents, amlodipine, a long-acting dihydropyridine calcium channel blocker (CCB), is widely prescribed due to its proven efficacy, tolerability, and ability to reduce blood pressure across diverse patient populations [4]. However, despite its broad clinical use, significant interindividual variability exists in response to amlodipine therapy, which poses challenges for personalized hypertension management [5, 6].

This variability in therapeutic response is influenced by multiple factors, including age, sex, comorbidities, and environmental conditions. In recent years, genetic factors have emerged as crucial determinants of drug efficacy and safety [7]. Pharmacogenomics, the study of how genes affect an individual's response to drugs, has provided insights into the mechanisms underlying variable responses to antihypertensive therapies. Specific genetic variants in key genes, such as *CYP3A4*, *RYR3*, *CACNA1C*, and *CACNA1D*, have been identified as playing a role in the metabolism, transport, and pharmacodynamic action of amlodipine [8, 9]. Population-specific differences further complicate the pharmacogenomics of amlodipine. Genetic variations can vary significantly across biogeographical groups, influencing the drug's efficacy and risk of adverse effects. For

example, certain alleles are more prevalent in African, European, or Asian populations, which may explain the observed differences in clinical outcomes [10, 11]. Understanding these associations is essential for developing targeted therapeutic strategies to optimize blood pressure control in diverse populations [12].

This review aims to explore the impact of genetic variants on amlodipine efficacy in hypertensive patients, with a focus on population-specific responses. By analyzing pharmacogenomic data and biogeographical variations, we seek to provide a comprehensive understanding of the role of genetics in antihypertensive therapy. Such insights will pave the way for precision medicine approaches, ensuring that patients receive the most effective and personalized treatment for hypertension.

## MATERIAL AND METHODS

### Study Design

This study adopts a bioinformatics-based approach to investigate the association between genetic variants and the efficacy of amlodipine in hypertensive patients. Data was extracted from publicly available pharmacogenomic databases, including PharmGKB and Gtex Portal, to identify relevant genetic variants, their functional significance, and population-specific distributions [13, 14].

### PharmGKB Database

PharmGKB (Pharmacogenomics Knowledge Base) was utilized to extract pharmacogenomic infor-

mation related to amlodipine. Pharmacogenomic associations were identified based on drug efficacy, genetic variant annotations, and related clinical outcomes. Search terms: “Amlodipine”, “Hypertension”, “Genetic variants”, “Population responses”. Filters Focused on efficacy outcomes and clinically relevant pharmacogenomic evidence.<sup>1516</sup>

### GTEx Portal

The GTEx (Genotype-Tissue Expression) Portal was used to analyze the expression levels of the genes associated with amlodipine efficacy across different tissues. Comparative analysis of expression levels was conducted to assess tissue-specific gene activity and its potential role in drug response [17, 18].

### Data Analysis

**Variant Selection:** Genetic variants were filtered based on their association with amlodipine efficacy (P-value < 0.05). Variants were prioritized based on their functional annotations (eg, coding regions, regulatory impact) [19, 20]. **Population-Specific Analysis:** Frequency data for the selected variants were extracted from PharmGKB and cross-referenced with biogeographical groups (eg, African, Asian, European) to

evaluate differences in genetic variant distributions<sup>15</sup>. **Data Visualization:** Results were presented using tables, heatmaps, and bar charts to illustrate variant distributions, functional impacts, and gene expression patterns across populations and tissues.

## RESULTS

The search for genes related to amlodipine response in the PharmGKB database resulted in 30 relevant genes. After elimination based on p-values greater than 0.05, and selection based on drug efficacy categories, only genes that showed significant potential in therapeutic response were retained.

### Identification of genetic variants associated with response to amlodipine in hypertension

This selection process resulted in 7 SNPs originating from 4 genes in Table 1 and 2. These genes were then taken and further analyzed to evaluate their role in influencing the effectiveness of amlodipine therapy in hypertensive patients. This further analysis is expected to reveal deep genetic relationships and improve understanding of more personalized therapy for hypertension.

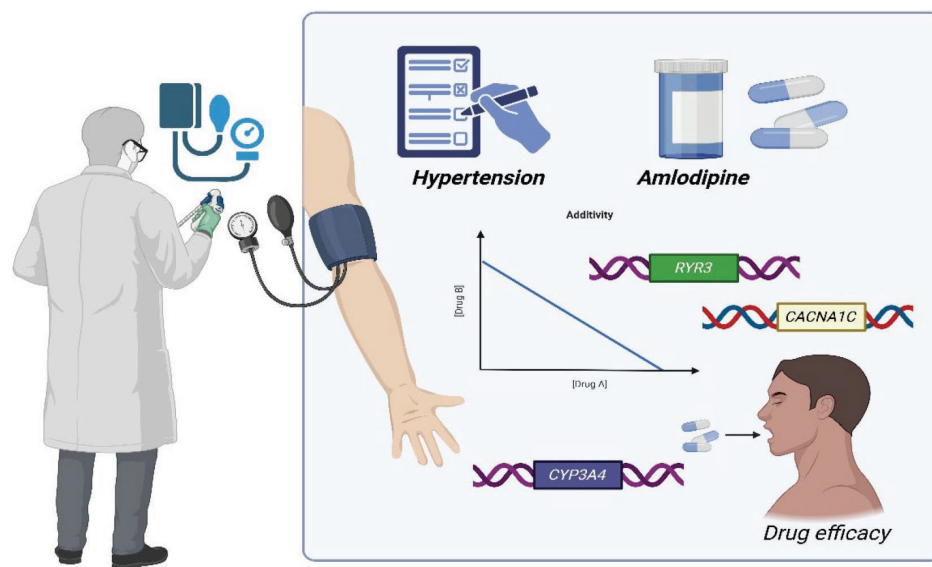


Fig. 1. Research method flowchart  
Created in <https://BioRender.com>

Table 1. Genetic variants associated with response to amlodipine in hypertension

Genes	Variants	P-Value	Cases
<i>CYP3A4</i>	rs2246709	0.01	145
<i>RYS3</i>	rs877087	0.04	1940
<i>CYP3A4</i>	rs2740574	0.02	61
<i>CACNA1C</i>	rs2239050	0.024	200
<i>CACNA1C</i>	rs2239050	0.05	53
<i>CACNA1C</i>	rs2239128	0.04	53
<i>CACNA1D</i>	rs312481	0.024	200

**Table 2. Association of Gene Variants with Amlodipine Efficacy in Different Ethnic Groups and Phenotype Categories**

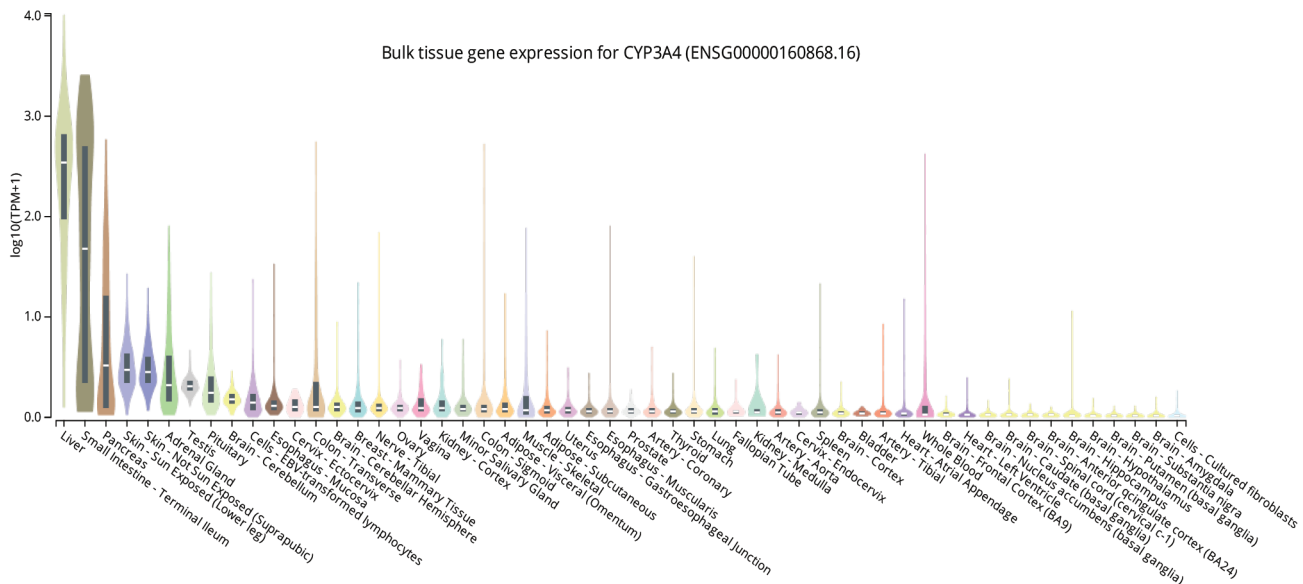
Drugs	Variants	Association	Biogeographical Groups	Phenotype Categories
Amlodipine	rs2246709	Genotypes AG + GG are associated with increased response to amlodipine in people with hypertension as compared to genotype AA.	African American/Afro-Caribbean	Efficacy
Amlodipine	rs877087	The TT genotype is associated with increased risk of Heart Failure when treated with amlodipine in people with Hypertension.	Multiple groups, 64.7% White, 32.1% Black, 0.3% American Indian/Alaskan native, 0.9% Asian/Pacific Islander, 2.1% other, 11.5% Hispanic	Efficacy
Amlodipine	rs2740574	Genotypes CT + TT are associated with increased response to amlodipine in women with hypertension as compared to genotype CC.	African American/Afro-Caribbean	Efficacy
Amlodipine	rs2239050	Genotype GG is associated with increased clinical benefit to amlodipine in people with Hypertension as compared to genotypes CC + CG.	Central/South Asian	Efficacy
Amlodipine	rs2239050	Genotype GG is associated with increased response to amlodipine and felodipine in people with hypertension as compared to genotype CG.	European	Efficacy
Amlodipine	rs2239128	Allele C is associated with increased response to amlodipine and felodipine in people with Hypertension as compared to allele T.	European	Efficacy
Amlodipine	rs312481	Genotype GG is associated with increased clinical benefit to amlodipine in people with hypertension as compared to genotypes AA + AG.	Central/South Asian	Efficacy

**Analysis of CYP3A4, RYR3, CACNA1D, CACNA1 gene expression in tissues and its relationship with the effectiveness of amlodipine in hypertension**

Amlodipine is a widely used calcium channel blocker and is effective in managing hypertension. However, interindividual variability in drug response is influenced by genetic factors. This analysis explores the tissue-specific expression of CYP3A4, RYR3, CAC-

NA1D, and CACNA1 genes, focusing on their functional roles in pharmacokinetics. and pharmacodynamics of amlodipine (Fig. 2).

The CYP3A4 gene is mainly expressed in the liver and small intestine, which plays an important role in amlodipine metabolism [21]. High hepatic expression facilitates the biotransformation of amlodipine to its inactive metabolites. Variability in CYP3A4 expression can alter drug plasma levels, affecting therapeutic outcomes. For



**Fig. 2. CYP3A4 gene expression in human body tissues**



The *CACNA1D* gene encodes the alpha-1 subunit of the L-type calcium channel, which is the primary target of amlodipine [29]. This channel plays an important role in regulating the entry of calcium ions into cells, which affects smooth muscle contraction and cellular electrophysiological function [30]. Expression analysis showed that the highest expression of *CACNA1D* was found in the cervix, accompanied by significant expression levels in cardiovascular tissues, such as the heart and blood vessels [31, 32]. Expression in the Cervix: High expression of *CACNA1D* in the cervix is likely related to the need for regulation of cervical smooth muscle contractions, especially in the context of reproductive functions such as labor. The role of L-type calcium channels in this tissue is to mediate coordinated calcium responses to physiological stimuli. Expression in Cardiovascular Tissues: In blood vessels and the heart, *CACNA1D* expression determines the effectiveness of L-type calcium channel blockade by amlodipine. These channels contribute directly to the regulation of vascular resistance and blood pressure. Relationship to Amlodipine Efficacy *CACNA1D* expression in cardiovascular tissues is an important factor in determining the clinical response to amlodipine: High Expression in Blood Vessels Increases sensitivity to calcium channel blockade, thereby enhancing the vasodilatory effect and lowering blood pressure. Low Expression in Blood Vessels May result in a weaker response to amlodipine, reducing the drug's effectiveness in lowering blood pressure [33].

The *CACNA1* gene encodes an additional subunit of the L-type calcium channel, which supports the stability and function of the channel, including in response to amlodipine [34]. Analysis showed the highest expression of this gene in the colon, reflecting its important role in the regulation of gastrointestinal

smooth muscle motility. Although expression in the colon is not directly related to blood pressure regulation, *CACNA1* expression in cardiovascular tissues, such as blood vessels, supports the efficacy of amlodipine by enhancing the function of calcium channels in reducing vascular resistance. Optimal expression levels may increase sensitivity to amlodipine, while low expression may reduce drug efficacy. In addition, expression in the colon may provide insight into potential gastrointestinal side effects of amlodipine use [35].

## DISCUSSION

Amlodipine works by inhibiting L-type calcium channels, which are regulated by genes such as *CACNA1D* and metabolized by the enzyme *CYP3A4*. This mechanism decreases peripheral vascular resistance, leading to lower blood pressure. However, the response to amlodipine varies significantly between individuals, which is largely due to genetic differences. Several genetic variants have been identified as determinants of response to amlodipine, including rs2246709, rs877087, rs2740574, and rs2239050, with different effects on efficacy and potential side effects. Several genetic variants have been identified to influence individual responses to amlodipine in hypertensive patients. The AG + GG genotype at rs2246709 in African-American/Afro-Caribbeans showed a better hypertensive response than the AA genotype, indicating an influence of this variation on calcium channel expression or function. In [36] contrast, the TT genotype at rs877087 found in diverse populations was associated with an increased risk of heart failure in hypertensive patients receiving amlodipine, reflecting a potential specific genetic side effect that requires clinical attention. In African-American/Afro-Caribbean women,

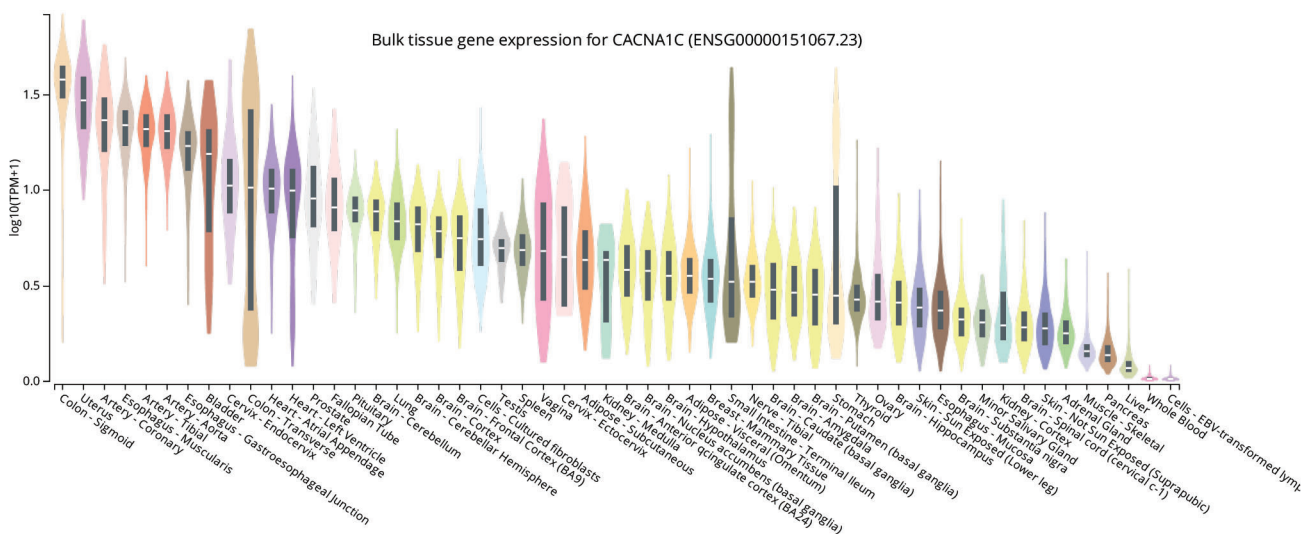


Fig. 5. CACNA1 gene expression in human body tissues

the CT + TT genotype at rs2740574 conferred a more optimal hypertensive response than the CC genotype, most likely through modulation of *CYP3A4* metabolizing enzyme activity [37].

Other genetic variations, such as the GG genotype at rs2239050, are associated with increased clinical benefit to amlodipine in Central/South Asian and European populations, suggesting that these variations may enhance drug efficacy through mechanisms affecting calcium channel transport or interactions. In Europeans, the C allele at rs2239128 increases the response to amlodipine and felodipine compared to the T allele, likely due to differences in calcium channel affinity [38]. In addition, the GG genotype at rs312481, which is common in Central/South Asians, is associated with greater clinical benefit compared to the AA + AG genotypes, suggesting a link to blood pressure regulation [39]. These variations highlight the importance of considering genetic factors in personalizing hypertension therapy with amlodipine [40, 41].

In terms of pharmacodynamics, *CACNA1C* and *CACNA1D* regulate the L-type calcium channels, which are the primary targets of amlodipine. SNPs such as rs2239050 (GG genotype) in Central/South Asian and European populations have been associated with increased drug efficacy, possibly due to enhanced calcium channel inhibition [31, 32]. Similarly, the C allele at rs2239128 is linked to greater response to amlodipine and felodipine in European populations, suggesting an effect on channel binding affinity. Moreover, variations in *RYR3* may contribute to adverse effects in certain individuals. The TT genotype at rs877087 has been associated with an increased risk of heart failure in hypertensive patients receiving amlodipine, potentially due to altered calcium signaling, which affects cardiac contractility. This suggests that pharmacogenomic screening could help identify patients at risk of cardiovascular side effects when prescribed amlodipine [39].

The different distribution of genetic variants across populations suggests that strategies for personalizing amlodipine therapy should be tailored based on ethnic and geographic factors. For example, SNPs associated with increased response to amlodipine are more common in Asian populations, which may provide a basis for considering dose adjustments or more appropriate antihypertensive therapy choices for these populations. Although associations between genetic variants and response to amlodipine have been identified, further validation through clinical studies is needed to confirm their therapeutic implications. Patient-based pharmacokinetic and pharmacodynamic studies would be helpful in confirming the specific role of the identified SNPs in drug metabolism and efficacy.

## CONCLUSION

Genetic variants of *CYP3A4* (rs2246709, rs2740574), *RYR3* (rs877087), *CACNA1C* (rs2239050, rs2239128), and *CACNA1D* (rs312481) play a role in determining the effectiveness of amlodipine in hypertensive patients. These findings emphasize the importance of pharmacogenomics in personalizing therapy, allowing treatment optimization based on population-specific genetic variations to increase effectiveness and reduce side effects.

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