Acta Biochimica Indonesiana

https://doi.org/10.32889/actabioina.237

RESEARCH ARTICLE

Open Access

Association between vitamin D receptor FokI polymorphism and hypertension in Indonesian ischemic stroke patients: a cross-sectional study

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ABSTRACT

Background: Vitamin D receptor (VDR) FokI polymorphism (rs2228570) affects VDR protein transcriptional activity and may influence hypertension risk through renin-angiotensin system modulation. However, evidence in Southeast Asian stroke populations remains limited.

Objective: To investigate the association between VDR FokI polymorphism and hypertension in Indonesian ischemic stroke patients.

Methods: This cross-sectional study enrolled 85 ischemic stroke patients (50 hypertensive, 35 normotensive) from Medan, Indonesia. VDR FokI genotypes (CC, CT, TT) were determined using PCR-RFLP. Association with hypertension was analyzed using chi-square test.

Results: Genotype distribution showed CC and CT at equal frequency (44.7% each) and TT at 10.6%, with corresponding C and T allele frequencies of 67.1% and 32.9%, respectively. Among hypertensive stroke patients, CT genotype predominated (52.0%), whereas CC genotype was most prevalent in normotensive patients (57.1%). Despite these distributional differences, no significant association was observed between VDR FokI polymorphism and hypertension (χ^2 = 3.732, p = 0.155).

Conclusion: VDR FokI polymorphism was not significantly associated with hypertension in Indonesian ischemic stroke patients, suggesting that genetic predisposition via this single polymorphism may be overshadowed by established stroke pathophysiology or complex gene-environment interactions in this specific clinical context.

Keywords: FokI polymorphism, vitamin D receptor, essential hypertension, ischemic stroke, genetic polymorphism

Introduction

Vitamin D, through its active metabolite 1α,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], functions as a crucial regulator of multiple physiological systems including cardiovascular homeostasis [1-2]. The biological effects of $1,25(OH)_2D_3$ are mediated through the vitamin D receptor (VDR), a nuclear transcription factor that modulates expression of approximately 3% of the human genome [3-4]. Extensive epidemiological evidence has linked vitamin D deficiency with increased cardiovascular disease risk, particularly hypertension and stroke [5-6]. Mechanistically, VDR serves as a negative endocrine regulator of the renin-angiotensin system (RAS); VDR-null mice demonstrate marked elevations in renin expression, plasma angiotensin II levels, and blood pressure [7-8], providing direct biological linkage between VDR and cardiovascular pathophysiology.

The human VDR gene harbors over 470 single nucleotide polymorphisms (SNPs), with FokI

[†] Yah Wardiah, PhD passed away before the publication of this article. She contributed substantially to the conception and design of the study and the initial drafting of the manuscript. At the time of her passing, she served as Chair of the PBBMI Medan Chapter and contributed to the development of the organization. All remaining authors take responsibility for the final version of the manuscript.

(rs2228570) being functionally unique as it affects the translation initiation site in exon 2 [9-11]. This results in VDR proteins differing by three amino acids (424 vs 427), with the shorter f allele (T allele) demonstrating enhanced transcriptional activity compared to the F allele (C allele) [12-13]. In contrast, other common VDR polymorphisms (BsmI, TaqI, ApaI) are located in intronic regions and may influence mRNA stability rather than protein function directly.

Recent investigations demonstrate population-specific associations between VDR polymorphisms and hypertension. While a 2024 meta-analysis showed BsmI polymorphism had the most consistent association with essential hypertension [14], FokI polymorphism evidence remains controversial. Khan et al. (2024) reported significant associations in Bangladeshi populations [15], and Indian studies demonstrated FF genotype conferring significant hypertension risk [16], while Caucasian studies reported null findings [17]. This inter-ethnic variability reflects differences in genetic background, environmental factors, and gene-environment interactions [11].

Hypertension represents the leading modifiable risk factor for cerebrovascular disease globally [18]. Stroke ranks as the second leading cause of mortality worldwide, with ischemic stroke accounting for 80-85% of cases [19-20]. In Indonesia, stroke prevalence increased from 8.3 to 12.1 per thousand (2007-2013), while hypertension prevalence reached 31.7% among adults [21-22]. Prabhakar et al. (2015) demonstrated that VDR FokI ff genotype conferred 2.97-fold increased ischemic stroke risk in Indians (95% CI: 1.16-7.63) [10]. However, studies examining VDR polymorphisms specifically in hypertensive stroke patients from Southeast Asian populations remain limited.

Despite established biological plausibility linking VDR to cardiovascular regulation via RAS suppression, and conflicting evidence across populations, the relationship between VDR FokI polymorphism and hypertension in ischemic stroke patients remains incompletely characterized in Southeast Asia, particularly Indonesia. This study aimed to determine VDR FokI genotype distribution (CC, CT, TT) and assess whether these genotypes differ significantly between hypertensive and normotensive Indonesian ischemic stroke patients.

Methods

Study design and participants

This hospital-based cross-sectional study investigated the association between VDR FokI polymorphism and hypertension in ischemic stroke patients at Haji Adam Malik General Hospital, Medan, Indonesia, between September and December 2018. The study utilized existing DNA samples from a previous doctoral research project, approved by the Health Research Ethical Committee, Faculty of Medicine, Universitas Sumatera Utara/H. Adam Malik General Hospital (ethical approval number: 195/TGL/KEPK FK USU-RSUP HAM/2018). All participants provided written informed consent prior to enrollment.

Sample size was calculated using the hypothesis testing formula for proportion: $n = (Z\alpha^2) \times P \times Q / d^2$, where $Z\alpha = 1.96$ ($\alpha = 0.05$, two-tailed), $P = 0.65$ (expected proportion of stroke patients with hypertension based on previous literature), $Q = 0.35$, and $d = 0.10$ (desired precision). This yielded a minimum of 85 participants, providing 80% power to detect moderate to large effect sizes (Cohen's $w \geq 0.3$) at $\alpha = 0.05$.

From 106 available DNA samples, 85 ischemic stroke patients meeting eligibility criteria were included. Inclusion criteria were: (1) ischemic stroke onset 3-14 days before enrollment, confirmed by clinical examination, neurological assessment, and computed tomography (CT) scan; (2) hospitalization in the integrated inpatient unit at Haji Adam Malik General Hospital; and (3) provision of written informed consent. Exclusion criteria included recurrent stroke, transient ischemic attack, hemorrhagic stroke, and known hemostatic disorders.

Variable definitions

Hypertension was defined according to 2017 ACC/AHA guidelines as systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥80

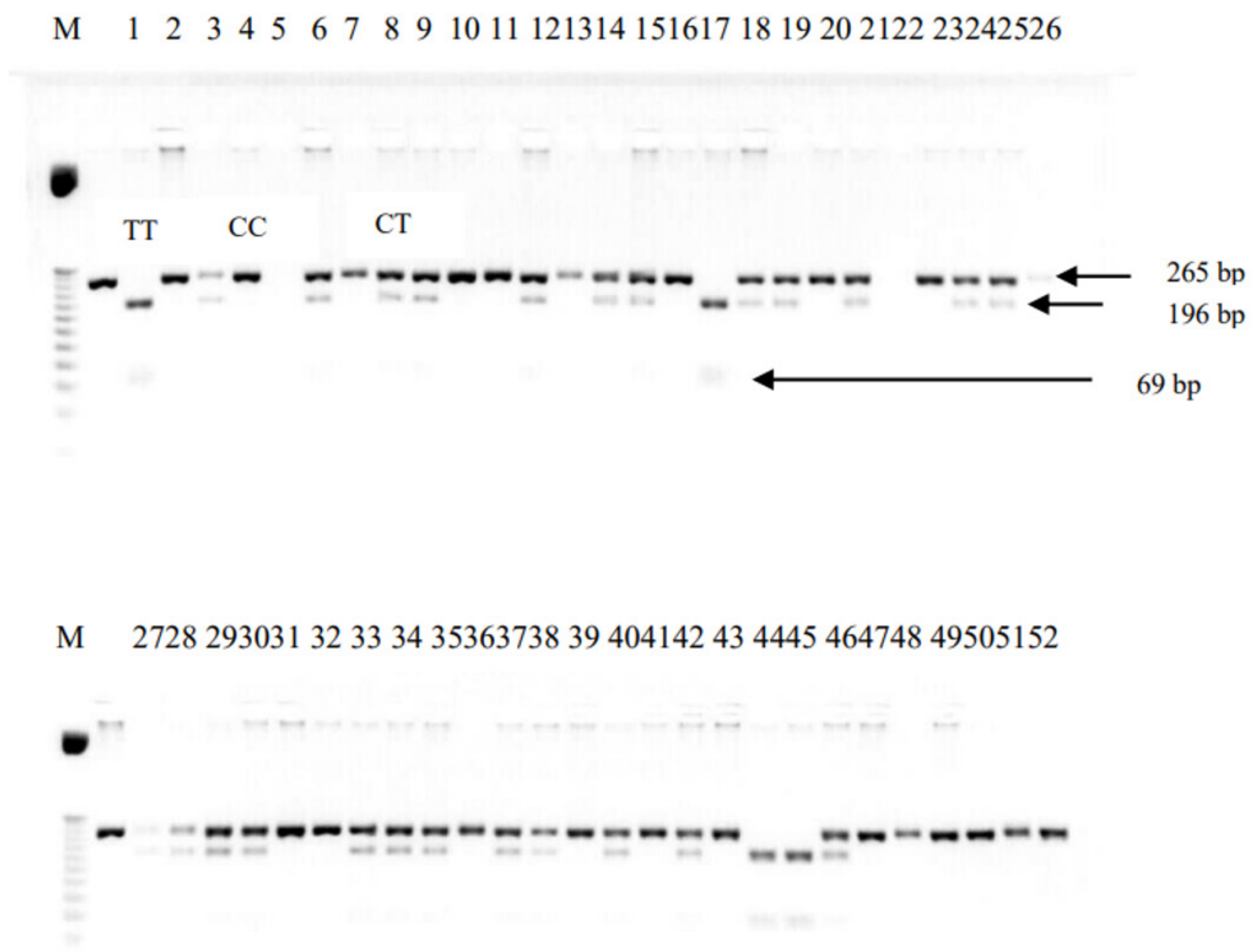

Figure 1. Representative RFLP analysis of VDR FokI polymorphism showing clear genotype separation on 4% agarose gel. M: 25 bp DNA ladder; CC genotype: single uncut band at 265 bp representing homozygous wild-type; TT genotype: two bands at 196 bp and 69 bp representing homozygous variant after complete digestion; CT genotype: three bands at 265 bp, 196 bp, and 69 bp representing heterozygous state with both wild-type and variant alleles. The gel image demonstrates reproducible and unambiguous genotype discrimination across all analyzed samples.

mmHg, while normotension was defined as systolic blood pressure <120 mmHg and diastolic blood pressure <80 mmHg [17]. Blood pressure was measured using standardized techniques after appropriate rest periods. VDR FokI polymorphism (rs2228570) genotypes were categorized as CC (homozygous wild-type), CT (heterozygous), or TT (homozygous variant).

DNA extraction and genotyping

Genomic DNA was extracted from peripheral blood samples using standard protocols. All molecular analyses were performed at the Integrated Laboratory, Faculty of Medicine, Universitas Sumatera Utara.

PCR amplification targeting the VDR FokI polymorphism region was performed using an Applied Biosystems Veriti 96-well Thermal Cycler. Each 25 μL reaction mixture contained 12.5 μL GoTaq® Green Master Mix (Promega, Madison, WI, USA), 8.5 μL nuclease-free water, 1.0 μL each of forward (5'-AGCTGGCCCTGGCACTGACTCTGCTCT-3') and reverse (5'-ATGGAAACACCTTGCTTCTTCTCCCTC-3') primers (10 pmol/μL; Integrated DNA Technologies, Coralville, IA, USA), and 2.0 μL template DNA (50-100 ng) [16].

Thermal cycling consisted of initial denaturation at 94°C for 45 seconds, followed by 35 cycles of denaturation (94°C, 45 seconds), annealing (60°C, 45 seconds), and extension (72°C, 45 seconds),

Table 1. Demographic and clinical characteristics of study participants (n=85)

Characteristic	n	%
Sex		
Male	42	49.4
Female	43	50.6
Age group		
<60 years	56	65.9
≥60 years	29	34.1
Hypertension Status		
Hypertensive	50	58.8
Normotensive	35	41.2

with final extension at 72°C for 5 minutes. PCR products (265 bp) were verified by electrophoresis on 2% agarose gel in 1× Tris-acetate-EDTA (TAE) buffer containing ethidium bromide (0.5 µg/mL), electrophoresed at 180 volts for 30 minutes, and visualized under UV transillumination.

RFLP analysis was performed using FastDigest FokI restriction enzyme (Thermo Fisher Scientific, Waltham, MA, USA). Each 10 µL digestion reaction contained 1.0 µL FastDigest buffer (10×), 3.8 µL nuclease-free water, 0.2 µL FokI enzyme (1 U/µL), and 5.0 µL PCR product. Reactions were incubated at 37°C for 2 hours, then analyzed on 4% agarose gel in 1× TAE buffer, electrophoresed at 180 volts for 30 minutes, and visualized under UV transillumination.

Genotypes were determined based on restriction fragment patterns: CC genotype showed a single uncut fragment at 265 bp; TT genotype showed two fragments at 196 bp and 69 bp; CT genotype showed three fragments at 265 bp, 196 bp, and 69 bp (Figure 1). Quality control included negative controls in each PCR run and random re-genotyping of 10% of samples, with 100% concordance.

Statistical analysis

Demographic and clinical data were extracted from medical records and analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Categorical variables (sex, hypertension status, VDR FokI genotypes) were presented as frequencies and percentages. Continuous variables (age) were categorized (<60 years vs ≥60 years) for presentation. The Kolmogorov-Smirnov test assessed normality of continuous variables. Hardy-Weinberg equilibrium (HWE) for genotype frequencies was assessed using chi-square goodness-of-fit test. Association between VDR FokI polymorphism and hypertension status was analyzed using Pearson's chi-square test. Statistical significance was set at $p < 0.05$ (two-tailed).

Results

Participant characteristics

A total of 85 ischemic stroke patients were included in this analysis, comprising 50 hypertensive patients (58.8%) and 35 normotensive patients (41.2%). The study population consisted of 42 males (49.4%) and 43 females (50.6%), demonstrating nearly equal sex distribution. Age distribution showed that 56 patients (65.9%) were below 60 years, while 29 patients (34.1%) were 60 years or older. The most frequently represented age groups were 56 and 57 years, each accounting for 8 patients (9.4%). Detailed demographic and clinical characteristics are presented in Table 1.

VDR FokI polymorphism distribution

Analysis of VDR FokI polymorphism revealed three distinct genotypes among participants. The CC genotype was identified in 38 patients (44.7%), comprising 19 males and 19 females. The heterozygous CT genotype was observed in

Table 2. Distribution of VDR FokI polymorphism genotypes among ischemic stroke patients (n=85)

VDR FokI genotype	n (%)
CC (homozygous wild-type)	38 (44.7)
CT (heterozygous)	38 (44.7)
TT (homozygous variant)	9 (10.6)
Total	**85 (100.0)**

Table 3. Association between VDR FokI polymorphism and hypertension status in ischemic stroke patients (n=85)

VDR FokI Genotype	Normotensive n (%)	Hypertensive n (%)
CC	20 (23.5)	18 (21.2)
CT	12 (14.1)	26 (30.6)
TT	3 (3.5)	6 (7.1)
Total	**35 (41.2)**	**50 (58.8)**

Note: χ^2 = 3.732, df = 2, p = 0.155 (Pearson's chi-square test)

38 patients (44.7%), consisting of 26 males and 12 females. The TT genotype was present in 9 patients (10.6%), including 6 males and 3 females. The distribution demonstrated equal prevalence of CC and CT genotypes, while TT genotype frequency was substantially lower. Genotype frequencies were in Hardy-Weinberg equilibrium (χ^2 = 0.847, p = 0.357), indicating no selection bias or genotyping errors. The distribution of genotypes is presented in Table 2.

Association between VDR FokI polymorphism and hypertension

The distribution of VDR FokI genotypes stratified by hypertension status is presented in Table 3. Among hypertensive ischemic stroke patients (n = 50), the CT genotype was most prevalent with 26 patients (30.6% of total population), followed by CC genotype with 18 patients (21.2%), and TT genotype with 6 patients (7.1%). In the normotensive group (n = 35), the CC genotype was most common with 20 patients (23.5% of total population), followed by CT genotype with 12 patients (14.1%), and TT genotype with 3 patients (3.5%).

Pearson's chi-square analysis revealed no statistically significant association between VDR FokI polymorphism and hypertension status in ischemic stroke patients (χ^2 = 3.732, df = 2, p = 0.155). The chi-square value of 3.732 with 2 degrees of freedom indicated that the distribution of VDR FokI genotypes did not differ significantly between hypertensive and normotensive stroke patients. This null finding suggests that VDR FokI polymorphism alone does not significantly contribute to hypertension risk in this specific patient population (Table 3).

RFLP analysis results

Restriction fragment length polymorphism analysis successfully differentiated the three VDR FokI genotypes based on characteristic DNA fragment patterns. The CC genotype exhibited a single uncut fragment at 265 bp, representing the wild-type allele resistant to FokI digestion. The TT genotype displayed complete digestion with two fragments at 196 bp and 69 bp, indicating homozygosity for the variant allele. The heterozygous CT genotype showed all three fragments (265 bp, 196 bp, and 69 bp), confirming the presence of both wild-type and variant alleles. Representative RFLP patterns for all three genotypes are illustrated in Figure 1, demonstrating clear and reproducible genotype discrimination across all 85 samples analyzed. The clarity of band separation on 4% agarose gel facilitated unambiguous genotype assignment.

Discussion

This study investigated the association between VDR FokI polymorphism and hypertension in Indonesian ischemic stroke patients. Our principal finding was the absence of a statistically significant association between VDR FokI genotypes (CC, CT, TT) and hypertension status among 85 ischemic stroke patients ($\chi^2 = 3.732$, $p = 0.155$). This null finding requires careful interpretation within the broader context of VDR genetics, cardiovascular disease mechanisms, and population-specific genetic architecture.

Our cohort showed balanced sex distribution (49.4% male, 50.6% female), with 65.9% of participants below 60 years and peak frequency at ages 56-57 years (9.4% each). This younger age profile may reflect increasing stroke incidence in developing countries, where cardiovascular risk factors manifest earlier due to lifestyle transitions and urbanization [23]. The high proportion of hypertensive patients (58.8%) aligns with established data identifying hypertension as the most significant modifiable risk factor for ischemic stroke globally, accounting for approximately 48% of population attributable risk [20,23].

The distribution of VDR FokI genotypes showed equal prevalence of CC and CT genotypes (44.7% each), with TT genotype least frequent (10.6%), demonstrating Hardy-Weinberg equilibrium ($p = 0.357$). This distribution differs from other Asian populations. Swapna et al. (2011) observed CC genotype predominance (45.4%) in an Indian population, followed by CT (42.1%) and TT (12.5%). Khan et al. (2024) reported different frequencies in Bangladeshi hypertensives: CC (31.5%), CT (48.6%), and TT (19.8%), reflecting distinct genetic backgrounds across South and Southeast Asian populations.

The FokI polymorphism (rs2228570) is functionally distinct from other common VDR polymorphisms (BsmI, ApaI, TaqI) due to its location in the translation initiation region of exon 2, resulting in VDR proteins differing by three amino acids at the N-terminus [12]. The T allele (f) produces a shorter VDR protein (424 amino acids) with enhanced transcriptional activity compared to the C allele (F) product (427 amino acids) [13], providing biological plausibility for FokI effects on VDR-mediated gene regulation, including renin-angiotensin system (RAS) suppression.

Our finding of no significant association ($p=0.155$) aligns with several previous investigations but contrasts with others, highlighting the complexity and context-dependency of this relationship. Our results are consistent with Cottone et al. (2015), who found no association between FokI and BsmI polymorphisms and hypertension in 143 Italian participants. A recent meta-analysis by Rahman et al. (2024) found no significant association between FokI polymorphism and essential hypertension in pooled analyses, though significant heterogeneity existed across studies [14].

Conversely, several studies have demonstrated significant associations. Khan et al. (2024) reported that FokI polymorphism was significantly associated with hypertension in Bangladeshis ($p < 0.01$), with CT and TT genotypes exhibiting higher systolic and diastolic blood pressure compared to CC genotype. Swapna et al. (2011) demonstrated that FF genotype and F allele significantly increased hypertension risk in 480 Indians [16]. Wang et al. (2013) reported that the ff genotype conferred a hazard ratio of 1.32 for hypertension development in men.

Several factors may explain these discrepancies. First, our study population consisted exclusively of ischemic stroke patients, a severe cardiovascular phenotype where the acute cerebrovascular event may overshadow subtle genetic contributions. Hypertension in stroke patients may be more strongly determined by cumulative cardiovascular risk factors and stroke-induced alterations rather than single genetic variants.

Second, the functional impact of VDR polymorphisms is likely modified by actual vitamin D status, which was not assessed in our study. Khan et al. (2024) demonstrated significantly lower 25-hydroxyvitamin D levels in hypertensive patients across all VDR genotypes, suggesting synergistic effects between vitamin D deficiency and VDR genetic variants [15]. Serra et al. (2024) demonstrated that vitamin D supplementation significantly reduced systolic blood pressure in individuals with both hypertension and hypovitaminosis D, suggesting VDR polymorphism effects may become apparent only in vitamin D deficiency contexts [24].

Third, ethnic and genetic background differences significantly influence VDR polymorphism-cardiovascular disease relationships. Our Indonesian population may possess distinct genetic architecture and gene-environment interactions compared to populations where significant associations were reported. The FokI polymorphism may be in linkage disequilibrium with different functional variants across populations. Furthermore, environmental factors including dietary patterns, sun exposure, and lifestyle factors differ markedly between Southeast Asian and other populations.

The biological plausibility of VDR polymorphisms affecting hypertension stems from VDR expression in cardiovascular tissues and its role in RAS regulation. Mechanistically, $1,25(OH)_2D_3$ suppresses renin gene transcription through direct VDR binding [7,27]. VDR-null mice demonstrate marked elevations in renal renin expression, plasma angiotensin II levels, and blood pressure, reversible by angiotensin-converting enzyme inhibitors [8]. Additionally, VDR signaling regulates parathyroid hormone secretion, influencing renal calcium and phosphate handling, sodium retention, and volume regulation [28].

Several studies have investigated VDR polymorphisms and stroke with varying results. Prabhakar et al. (2015) demonstrated that VDR FokI ff genotype conferred 2.97-fold increased risk for ischemic stroke in Indians [10]. However, our study examined the hypertension-FokI relationship within stroke patients rather than stroke susceptibility per se.

This study possesses several strengths including well-defined inclusion criteria ensuring homogeneous patient population, established PCR-RFLP techniques with quality control, statistically calculated sample size, and verification of Hardy-Weinberg equilibrium indicating absence of systematic errors.

However, several important limitations must be acknowledged. First, the cross-sectional design precludes causal inference. Second, lack of serum 25-hydroxyvitamin D measurement prevents assessment of gene-environment interactions. Third, the sample size may have been insufficient for detecting modest genetic effects typical of complex traits. Fourth, only the FokI polymorphism was examined; other VDR polymorphisms and haplotype analysis may provide additional insights. Fifth, important confounders including body mass index, physical activity, dietary patterns, comorbidities, medication use, and hypertension duration were not systematically assessed. Sixth, single-center recruitment potentially limits generalizability. Seventh, lack of vitamin D supplementation history and sun exposure data prevents assessment of environmental modifiers.

The clinical implications suggest that VDR FokI genotyping alone appears unlikely to offer utility for hypertension risk stratification in ischemic stroke populations. However, vitamin D status assessment and targeted supplementation in stroke patients with hypovitaminosis D warrants investigation, given meta-analytic evidence supporting blood pressure reduction with vitamin D supplementation [24].

Future research should encompass larger, multi-center studies across diverse Southeast Asian populations to enhance statistical power and generalizability. Investigations should incorporate multiple VDR polymorphisms with haplotype analysis, prospective cohort designs examining VDR polymorphisms as predictors of incident hypertension or stroke recurrence, integration of serum 25-hydroxyvitamin D levels and calcium metabolism markers, intervention studies examining whether vitamin D supplementation effects differ by VDR genotype, and genome-wide association studies to better capture the complex genetic architecture underlying hypertension in stroke populations.

Conclusion

This study found no significant association between VDR FokI polymorphism and hypertension among Indonesian ischemic stroke patients ($p = 0.155$). These findings suggest that VDR FokI polymorphism alone does not serve as a major determinant of hypertension risk in this population, possibly due to predominant stroke pathophysiology, unmeasured gene-environment interactions, or population-specific genetic architecture. Given established biological roles of vitamin D-VDR in cardiovascular regulation and conflicting results across populations, future research incorporating larger sample sizes, multiple VDR polymorphisms, vitamin D status assessment, and diverse ethnic populations is essential to elucidate the complex interplay between VDR genetics and cardiovascular disease risk.

Acknowledgment

None.

Funding

None.

Author Contributions

Conceptualization: RA, YS. Methodology: RA, YS. Investigation: RA, CAA. Data curation: RA, CAA. Formal analysis: RA, CAA. Validation: CAA, YS. Visualization: RA. Project administration: RA. Resources: YS. Supervision: YS. Writing – original draft: RA. Writing – review & editing: RA, CAA, YS. All authors have read and approved the final manuscript.

Declaration of interest

The authors declare no conflicts of interest with any private, public, or academic entities related to the content of this manuscript.

Received: January 3, 2026
Revised: February 5, 2026
Accepted: February 15, 2026
Published: February 16, 2026

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