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Research Article

Prevalence of CYP2C9 polymorphisms and predicted metabolizer phenotypes in Balinese patients receiving phenytoin therapy at Buleleng Regency General Hospital, Indonesia

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ABSTRACT

CYP2C9 polymorphisms contribute to interindividual variability in phenytoin metabolism, a medication characterized by a narrow therapeutic index. This study aimed to determine the prevalence of CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) polymorphisms and to classify CYP2C9 related predicted metabolizer phenotypes, namely Extensive Metabolizer (EM), Intermediate Metabolizer (IM), and Poor Metabolizer (PM), among Balinese patients receiving phenytoin therapy at Buleleng Regency General Hospital, Indonesia. A non-phenytoin Balinese group was included as a population reference comparator to describe the background distribution of CYP2C9 genetic variation. This observational cross-sectional study was conducted among 200 Balinese participants, consisting of 100 phenytoin users and 100 non-phenytoin participants as a population reference group. Genotyping of CYP2C9*2 and CYP2C9*3 was performed using the Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP) method. Genotype and metabolizer phenotype distributions were analyzed descriptively, while differences in distribution between phenytoin users and non-phenytoin participants were evaluated using the Chi-square test. Among phenytoin users, no CYP2C9*2 polymorphism was detected, with all participants carrying the *1/*1 genotype. In contrast, CYP2C9*3 demonstrated greater genotype variability, with genotype frequencies of *1/*1 (41%), *1/*3 (42%), and *3/*3 (17%). Based on the variant-specific classification used in this study, these genotypes corresponded to the Extensive Metabolizer (EM), Intermediate Metabolizer (IM), and Poor Metabolizer (PM) phenotypes, respectively. No significant difference was observed in CYP2C9*3 genotype distribution or predicted metabolizer phenotype classification between phenytoin users and non-phenytoin participants ($p = 0.739$). CYP2C9*3 was the predominant decreased-function variant among Balinese participants receiving phenytoin therapy, whereas CYP2C9*2 was detected at a very low frequency and contributed minimally to CYP2C9 metabolic variability. The similar distribution of CYP2C9 genotypes and metabolizer phenotypes between phenytoin users and non-phenytoin participants suggests that the observed pattern likely reflects the underlying genetic characteristics of the Balinese population rather than the effect of phenytoin exposure. These findings provide pharmacogenetic baseline data on CYP2C9 distribution and predicted metabolizer phenotype variability, which may support future investigations evaluating phenytoin plasma concentrations and therapeutic response in the Balinese population.

Keywords:
CYP2C9; Phenytoin; Pharmacogenetics; Polymorphism; Metabolizer phenotype; Balinese; PCR-RFLP

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1. INTRODUCTION

Phenytoin remains an important antiseizure medication in clinical practice, but its safe and effective use is complicated by a narrow therapeutic index, nonlinear Michaelis-Menten pharmacokinetics, and marked interindividual variability in exposure. Small changes in dose or intrinsic clearance can cause disproportionate changes in plasma concentration, thereby increasing the risk of concentration-related neurotoxicity, gingival enlargement, cerebellar symptoms, or treatment failure when exposure is inadequate (Patocka et al., 2020; Sumarno et al., 2023; Harahap et al., 2024). These characteristics make phenytoin a clinically relevant model drug for pharmacogenetic assessment.

CYP2C9 is the principal enzyme involved in phenytoin oxidation, with CYP2C19 contributing to a smaller extent. Functional CYP2C9 variants may reduce enzymatic activity, delay phenytoin clearance, and increase the probability of elevated drug concentrations. Current pharmacogenetic guidance recognizes CYP2C9 genotype as an actionable factor in phenytoin dose individualization, particularly when decreased-function alleles are present (Karnes et al., 2021). Recent systematic evidence on antiseizure drugs also supports the clinical relevance of pharmacogenetic variants in explaining variability in antiseizure medication exposure (Milosavljevic et al., 2024; De Bellis et al., 2025).

Among the most widely studied CYP2C9 decreased-function alleles are CYP2C9*2 (rs1799853; C430T; Arg144Cys) and CYP2C9*3 (rs1057910; A1075C; Ile359Leu). The CYP2C9*3 allele is particularly important in Asian populations, where it is generally more relevant than CYP2C9*2, whereas CYP2C9*2 is more frequently reported in several European and Middle Eastern populations (Zhou et al., 2023; Biswas et al., 2025). These interpopulation differences mean that genotype prevalence cannot be generalized across ethnic groups without local evidence.

Indonesia is characterized by substantial ethnic, geographic, and genetic diversity. Previous Indonesian data remain limited and are concentrated in selected populations, with reports suggesting that CYP2C9*3 may be more common than CYP2C9*2 in some Indonesian ethnic groups (Niruri et al., 2021; Tuba et al., 2021). However, evidence for Balinese populations, particularly among patients receiving phenytoin, is still insufficient. This gap is important because local CYP2C9 prevalence data are required to characterize genetic variation and support future pharmacogenetic evaluation in Balinese populations.

Therefore, this study aimed to determine the prevalence of CYP2C9*2 and CYP2C9*3 polymorphisms and to classify CYP2C9 related predicted metabolizer phenotypes extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) among Balinese patients receiving phenytoin therapy at Buleleng Regency General Hospital. A non-phenytoin Balinese group was included as a population reference comparator to clarify whether the observed polymorphism distribution reflects background population variation rather than phenytoin exposure itself.

2. MATERIALS AND METHODS

2.1. Study design, setting, and participants

This was an observational cross-sectional pharmacogenetic study conducted at Buleleng Regency General Hospital, Bali, Indonesia. The study included 200 participants consisting of 100 Balinese patients receiving phenytoin therapy and 100 Balinese non-phenytoin participants as a population reference comparator. The non-phenytoin group was not designed as an exposure group for clinical outcome evaluation; rather, it served to compare the background distribution of CYP2C9 variants in Balinese individuals. Eligible participants were aged 20–60 years, were ethnically Balinese based on at least three generations of ancestry, included patients receiving phenytoin therapy and non-phenytoin participants as a reference group, had complete medical records, including patient identity, medical history, and medication history, sufficient for eligibility assessment, and provided written informed consent. Participants were excluded if biological samples were inadequate for genotyping, ancestry information could not be verified, or they had a history of liver dysfunction.

2.2. Materials and instruments

The main reagents and materials used in this study included Cell Lysis Solution (A7122, Promega, USA), Nuclei Lysis Solution (Promega, USA), Protein Precipitation Solution (Promega, USA), DNA Rehydration Solution from the Wizard Genomic DNA Purification Kit (Promega, USA), Taq Buffer (10X, Thermo Scientific), dNTP Mix (Thermo Scientific), Proteinase K (Sigma-Aldrich), Buffer R, Buffer Anza, isopropanol (Sigma-Aldrich, ≥99.5%), ethanol (Merck Emsure, 96–100%), CYP2C9*2 and CYP2C9*3 primers, restriction enzymes AvaII and NsiI, agarose gel, electrophoresis buffer, staining reagents, EDTA blood collection tubes.

The instruments used in this study included a deep freezer, centrifuge, vortex mixer (Thermo Scientific), microcentrifuge (Cleaver CSLQSPIN), Thermal Cycler PCR System 2700 (Applied Biosystems), Mupid-exU electrophoresis apparatus, UV-Vis spectrophotometer, water bath, Ohaus PA214 digital balance, micropipettes (Socorex 100 µL, Eppendorf 200 µL and 1000 µL), micropipette tips, conical tubes, Eppendorf tubes (1.5 mL), standard laboratory glassware and Gel Documentation (Gel Doc) system.

Table 1. Methodological workflow for CYP2C9 pharmacogenetic analysis.

Step 1	Eligible participants screened at Buleleng Regency General Hospital
	↓
Step 2	Written informed consent and confirmation of Balinese ancestry across at least three generations
	↓
Step 3	Allocation by clinical exposure: phenytoin users (n=100) and non-phenytoin reference group (n=100)
	↓
Step 4	EDTA blood collection and genomic DNA extraction
	↓
Step 5	DNA purity/concentration assessment and PCR amplification of CYP2C9*2 and CYP2C9*3 targets
	↓
Step 6	AvaII/NsiI RFLP digestion and agarose gel electrophoresis
	↓
Step 7	Genotype calling → Allele-frequency estimation → Metabolizer phenotype assignment (EM, IM, PM) → Group-comparison analysis → Odds Ratio (OR) analysis → Hardy–Weinberg Equilibrium (HWE) analysis

2.3. Sample collection and DNA isolation

Participants who met the inclusion and exclusion criteria were recruited from Buleleng Regency General Hospital. Blood samples were collected from September to December 2025 as 3 mL of whole blood in EDTA tubes. Samples were stored at 4°C prior to DNA extraction. Genomic DNA was isolated from whole blood using the Promega DNA isolation protocol. The procedure included cell lysis, nuclear lysis, protein precipitation, DNA precipitation, DNA washing, and DNA rehydration. DNA concentration and purity were evaluated using UV-Vis spectrophotometry. Samples with acceptable purity based on the A260/A280 ratio were further subjected to PCR amplification.

2.4. Polymerase chain reaction (PCR) amplification

PCR amplification was performed using primers targeting CYP2C9*2 and CYP2C9*3. For CYP2C9*2, the forward primer was 5'-TACAAATACAATGAA AATATCATG-3' and the reverse primer was 5'-CTA ACAACCAGACTCATAATG-3'. For CYP2C9*3, the forward primer was 5'-AATAATAATATGCACGAG GTCCAGAGATGC-3' and the reverse primer was 5'-GATACTATGAATTTGGGACTTCG-3'. PCR cycling consisted of initial denaturation at 95°C for 5 min; 35 cycles of denaturation at 95°C, annealing at 47.2°C for CYP2C9*2 and 52°C for CYP2C9*3, and elongation at 72°C; followed by final elongation at 72°C for 10 min. The target amplicon sizes were 690 bp for CYP2C9*2 and 141 bp for CYP2C9*3.

2.5. Restriction fragment length polymorphism (RFLP) genotyping and phenotype assignment

Genotyping of the CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910) alleles was performed using the Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR–RFLP) method with the restriction enzymes AvaII and NsiI, respectively (Khaleqsefat et al., 2017; Tuba et al., 2021). The PCR amplicon for CYP2C9*2 was 690 bp and, following AvaII digestion, produced fragments of 521 bp and 169 bp. The PCR amplicon for CYP2C9*3 was 141 bp and, following NsiI digestion, yielded fragments of 112 bp and 29 bp (Khaleqsefat et al., 2017; Tuba et al., 2021). This assay was designed to detect the 430C>T (Arg144Cys) substitution in CYP2C9*2 and the 1075A>C (Ile359Leu) substitution in CYP2C9*3, both of which are associated with reduced CYP2C9 enzymatic activity and may influence phenytoin metabolism (Brehm et al., 2013; Balakrishnan et al., 2021).

For CYP2C9*2, the RFLP reaction mixture consisted of 4 µL of PCR product, 2 µL of Buffer R, 0.5 µL of AvaII restriction enzyme, 7.5 µL of nuclease-free water, and 6 µL of ddH_2O, giving a total reaction volume of 20 µL. For CYP2C9*3, the reaction mixture comprised 5 µL of PCR product, 1.25 µL of Buffer Anza, 1.25 µL of NsiI restriction enzyme, 7.5 µL of nuclease-free water, and 5 µL of ddH_2O, resulting in a total reaction volume of 20 µL. The digestion procedures were performed according to protocols modified from Khaleqsefat et al. (2017) and Tuba et al. (2021). The digested products were subsequently separated by electrophoresis on 2.5% agarose gel containing ethidium bromide at 100 V for approximately 30 minutes and visualized using a Gel Documentation (Gel Doc) system.

2.6. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 27 and cross-checked using manual calculations. Categorical variables are presented as frequency and percentage. Allele frequency was calculated using the standard gene-counting method: variant allele frequency = (number of heterozygotes + 2 × number of homozygous variants) / (2 × total participants).

Table 2. Characteristics of study participants.

Variable	Category	Phenytoin users (n = 100), n (%)	Non-phenytoin reference (n = 100), n (%)	Total (N = 200), n (%)
Age (years)	Mean ± SD	39.97 ± 10.19	39.15 ± 11.01	–
	20–40	54 (54.0)	51 (51.0)	105 (52.5)
	40–60	46 (46.0)	49 (49.0)	95 (47.5)
	Total	100 (100.0)	100 (100.0)	200 (100.0)
Gender	Female	55 (55.0)	67 (67.0)	122 (61.0)
	Male	45 (45.0)	33 (33.0)	78 (39.0)
	Total	100 (100.0)	100 (100.0)	200 (100.0)
Medical history	Epilepsy	70 (70.0)	NA	NA
	Post-stroke epilepsy / Stroke with seizures	17 (17.0)	NA	NA
	Other neurological disorders	13 (13.0)	NA	NA
	Total	100 (100.0)	NA	NA
Medication history	Phenytoin monotherapy	90 (90.0)	NA	NA
	Phenytoin + Phenobarbital	10 (10.0)	NA	NA
	Total	100 (100.0)	NA	NA

NA: not applicable; medical history and medication history were assessed only among phenytoin users.

Approximate 95% confidence intervals (95% CI) were calculated for key proportions. Hardy-Weinberg equilibrium (HWE) was evaluated using observed and expected genotype frequencies. CYP2C9*3 genotype and metabolizer distributions between phenytoin users and non-phenytoin participants were compared using Pearson's Chi-square test because expected counts met the test assumptions. A p-value <0.05 was considered statistically significant (McHugh, 2013).

3. RESULTS

3.1. Participant characteristics

A total of 200 Balinese participants were included in this study, consisting of 100 phenytoin users and 100 non-phenytoin participants. The mean age was 39.97 ± 10.19 years among phenytoin users and 39.15 ± 11.01 years among non-phenytoin participants. Most participants were aged 20–40 years (52.5%) and were female (61.0%). Among phenytoin users, epilepsy was the most common clinical indication (70.0%), followed by post-stroke epilepsy/stroke with seizures (17.0%) and other neurological disorders (13.0%). Most patients received phenytoin as monotherapy (90.0%), while 10.0% received combination therapy with phenobarbital.

3.2. DNA isolation, PCR amplification, and RFLP visualization

Genomic DNA was successfully isolated from all 200 samples. The PCR products showed expected target bands for CYP2C9*2 (690 bp) and CYP2C9*3 (141 bp), indicating successful amplification of the target regions. RFLP visualization confirmed distinguishable digestion patterns for wild-type, heterozygous, and homozygous variant genotypes. The representative electrophoresis results generated from the present study are shown in Figures 1–4.

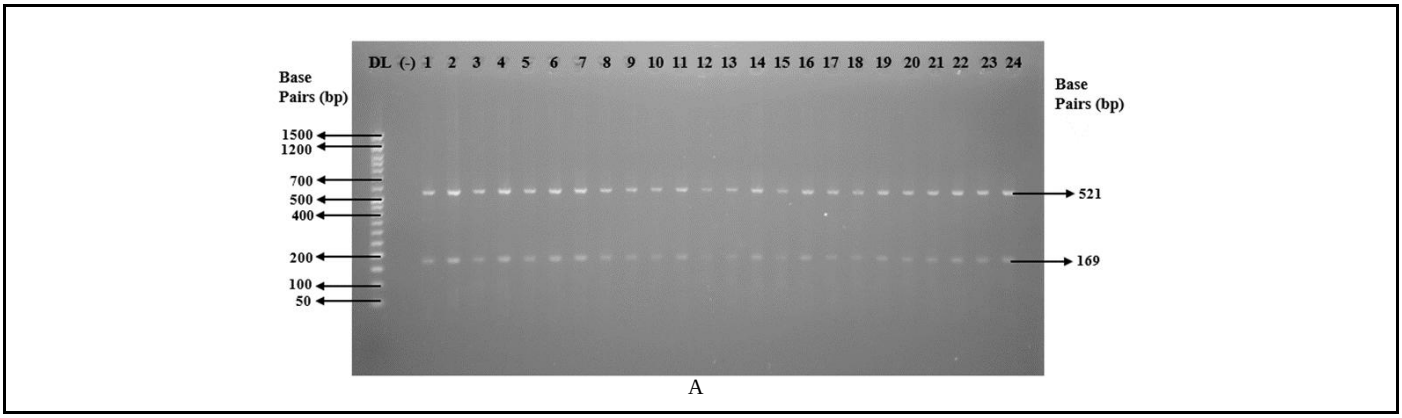
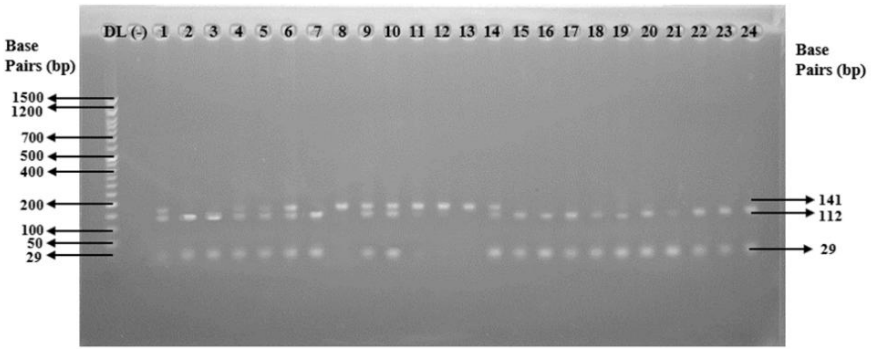
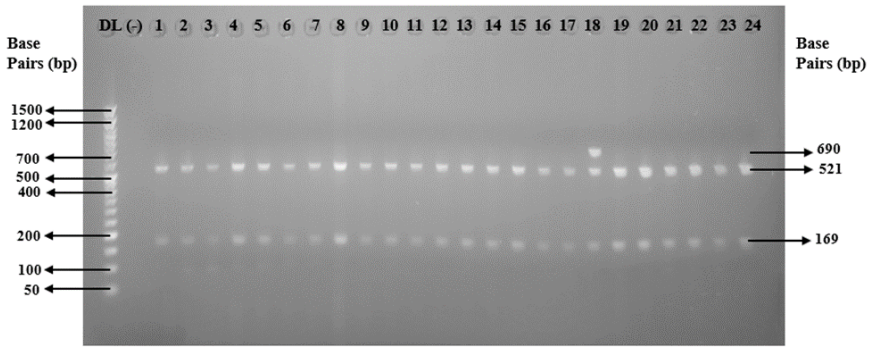


Figure 1. Representative RFLP profile of CYP2C9*2 using AvaII in phenytoin-user samples.



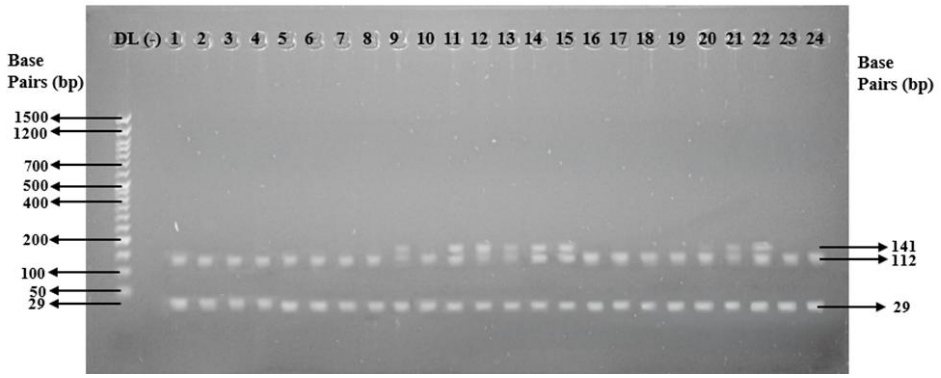
B

Figure 2. Representative RFLP profile of CYP2C9*3 using NsiI in phenytoin-user samples.



A

Figure 3. Representative RFLP profile of CYP2C9*2 using AvaII in non-phenytoin reference samples.



B

Figure 4. Representative RFLP profile of CYP2C9*3 using NsiI in non-phenytoin reference samples.

3.3. Distribution of CYP2C9 Genotypes and metabolizer phenotypes

The CYP2C9 genotype distribution among phenytoin users showed that all participants (100%; n = 100) carried the *1/*1 genotype (wild-type) for CYP2C9*2, with no CYP2C9*2 variant allele detected. In contrast, CYP2C9*3 demonstrated greater genotype variability, with distributions of *1/*1 (41%), *1/*3 (42%), and *3/*3 (17%). These findings indicate that CYP2C9*3 polymorphism was more frequently observed than CYP2C9*2 among phenytoin users.

Among non-phenytoin participants, the CYP2C9*2 genotype distribution was predominantly *1/*1 (99%), with only 1% carrying the *1/*2 genotype and no *2/*2 genotype detected. Meanwhile, the CYP2C9*3 genotype distribution consisted of *1/*1 (36%), *1/*3 (47%), and *3/*3 (17%), indicating that CYP2C9*3 polymorphism was more frequently observed than CYP2C9*2 in this group.

Table 3. Frequencies of CYP2C9*2 and CYP2C9*3 polymorphisms among phenytoin users

CYP2C9 PCR Product	N (%)	CYP2C9 RFLP Fragment (bp)	CYP2C9 Genotype	Genotype Classification	n (%)
690 bp	100 (100%)	521 + 169	*1/*1	Wild-type	100 (100%)
		690 + 521 + 169	*1/*2	Heterozygous variant	0 (0%)
		690	*2/*2	Homozygous variant	0 (0%)
141 bp	100 (100%)	112 + 29	*1/*1	Wild-type	41 (41%)
		141 + 112 + 29	*1/*3	Heterozygous variant	42 (42%)
		141	*3/*3	Homozygous variant	17 (17%)

Table 4. Frequencies of CYP2C9*2 and CYP2C9*3 polymorphisms among non-phenytoin participants.

CYP2C9 PCR Product	N (%)	CYP2C9 RFLP Fragment (bp)	CYP2C9 Genotype	Genotype Classification	n (%)
690 bp	100 (100%)	521 + 169	*1/*1	Wild-type	99 (99%)
		690 + 521 + 169	*1/*2	Heterozygous variant	1 (1%)
		690	*2/*2	Homozygous variant	0 (0%)
141 bp	100 (100%)	112 + 29	*1/*1	Wild-type	36 (36%)
		141 + 112 + 29	*1/*3	Heterozygous variant	47 (47%)
		141	*3/*3	Homozygous variant	17 (17%)

The combined distribution of CYP2C9*2 and CYP2C9*3 genotypes showed that the CYP2C9 *1/*1 genotype, corresponding to the predicted Extensive Metabolizer (EM) phenotype, was identified in 77 participants (38.5%), consisting of 41 phenytoin users and 36 non-phenytoin participants. The predicted Intermediate Metabolizer (IM) phenotype was mainly represented by the CYP2C9 *1/*3 genotype, which was observed in 88 participants (44.0%), while the CYP2C9 *1/*2 genotype was identified in only one participant (0.5%). The predicted Poor Metabolizer (PM) phenotype was exclusively observed in participants with the CYP2C9 *3/*3 genotype, accounting for 34 participants (17.0%). No participants carried the CYP2C9 *2/*2 or CYP2C9 *2/*3 genotypes. Overall, the distribution of predicted CYP2C9 metabolizer phenotypes in this Balinese population was predominantly influenced by the presence of the CYP2C9*3 allele, whereas the CYP2C9*2 allele was rarely observed and appeared to have a minimal contribution to the overall genetic variation of CYP2C9 in the study population.

When genotype-specific predictions were summarized across all 200 participants, CYP2C9*2 was predominantly represented by the *1/*1 genotype category (199/200; 99.5%), corresponding to the predicted Extensive Metabolizer (EM) classification applied in this study. Only one participant carried the *1/*2 genotype, corresponding to the predicted Intermediate Metabolizer (IM) classification, while no *2/*2 genotype was detected. In contrast, CYP2C9*3 demonstrated greater genotype-based variability, with predicted EM, IM, and PM classifications observed in 77 (38.5%), 89 (44.5%), and 34 (17.0%) participants, respectively. These classifications represent genotype-based predictions derived from CYP2C9*2 and CYP2C9*3 variants and should not be interpreted as direct measurements of CYP2C9 enzymatic activity or clinical phenytoin response.

Table 5. Distribution of predicted metabolizer phenotypes based on CYP2C9 genotypes among phenytoin users and non-phenytoin participants.

CYP2C9*2	CYP2C9*3	Combined CYP2C9	Predicted CYP2C9 Metabolizer Phenotype	Phenytoin Users (n=100)	Non-Phenytoin Participants (n=100)	Total (N=200)
***1/*1**	*1/*1	*1/*1	Extensive Metabolizer (EM)	41 (41.0%)	36 (36.0%)	77 (38.5%)
***1/*2**	*1/*1	*1/*2	Intermediate Metabolizer (IM)	0 (0.0%)	1 (1.0%)	1 (0.5%)
***1/*1**	*1/*3	*1/*3	Intermediate Metabolizer (IM)	42 (42.0%)	46 (46.0%)	88 (44.0%)
***2/*2**	*1/*1	*2/*2	Poor Metabolizer (PM)	0 (0.0%)	0 (0.0%)	0 (0.0%)
***1/*2**	*1/*3	*2/*3	Poor Metabolizer (PM)	0 (0.0%)	0 (0.0%)	0 (0.0%)
***1/*1**	*3/*3	*3/*3	Poor Metabolizer (PM)	17 (17.0%)	17 (17.0%)	34 (17.0%)
Total				100 (100%)	100 (100%)	200 (100%)

Table 6. Distribution of predicted CYP2C9 metabolizer phenotypes.

Variant	Genotype	Genotype interpretation	Metabolizer type	n (%)
CYP2C9*2	*1/*1	Wild-type	Extensive Metabolizer (EM)	199 (99.5)
	*1/*2	Heterozygous variant	Intermediate Metabolizer (IM)	1 (0.5)
	*2/*2	Homozygous variant	Poor Metabolizer (PM)	0 (0.0)
CYP2C9*3	*1/*1	Wild-type	Extensive Metabolizer (EM)	77 (38.5)
	*1/*3	Heterozygous variant	Intermediate Metabolizer (IM)	89 (44.5)
	*3/*3	Homozygous variant	Poor Metabolizer (PM)	34 (17.0)

3.4. Comparison of CYP2C9 genotype distribution and predicted metabolizer phenotype classification among study groups

The distribution of CYP2C9*3 genotypes showed a similar pattern between phenytoin users and non-phenytoin participants. Among phenytoin users, the *1/*1 (EM), *1/*3 (IM), and *3/*3 (PM) genotypes were observed in 41%, 42%, and 17% of participants, respectively, whereas the corresponding frequencies among non-phenytoin participants were 36%, 47%, and 17%. No significant difference was observed between the two groups based on the Chi-square test ($p = 0.739$), indicating that CYP2C9*3 genotype distribution did not differ statistically between phenytoin users and non-phenytoin participants. The comparative analysis focused on CYP2C9*3 because this allele was more prevalent and represented the major contributor to CYP2C9 metabolizer phenotype variability, whereas CYP2C9*2 was detected at a very low frequency.

3.5. Odds ratio (OR) analysis

Odds ratio (OR) analysis showed that participants with normal genotypes had 1.235-fold higher odds of being phenytoin users compared with those carrying variant genotypes. Similarly, participants classified as Extensive Metabolizers (EM) had 1.235-fold higher odds of being phenytoin users compared with non-EM participants. However, the 95% confidence interval for both analyses (0.698–2.186) included the null value of 1, indicating that neither association was statistically significant.

3.6. Hardy-Weinberg equilibrium analysis

Hardy–Weinberg equilibrium (HWE) analysis demonstrated that the genotype distributions of CYP2C9*2 and CYP2C9*3 were consistent with HWE in both phenytoin users and non-phenytoin participants. Among phenytoin users, CYP2C9*2 showed only the *1/*1 genotype (100%), with a χ^2 value of 0.000. CYP2C9*3 showed genotype distributions of *1/*1 (41%), *1/*3 (42%), and *3/*3 (17%), with a χ^2 value of 1.181. Among non-phenytoin participants, CYP2C9*2 genotype frequencies were *1/*1 (99%), *1/*2 (1%), and *2/*2 (0%), with a χ^2 value of 0.003, while CYP2C9*3 showed *1/*1 (36%), *1/*3 (47%), and *3/*3 (17%), with a χ^2 value of 0.062. All calculated χ^2 values were lower than the critical value of 3.841 ($df=1$; $\alpha=0.05$), indicating no significant deviation from Hardy–Weinberg equilibrium.

4. DISCUSSION

This study determined the prevalence of CYP2C9*2 and CYP2C9*3 polymorphisms and the distribution of predicted CYP2C9 metabolizer phenotypes among Balinese patients receiving phenytoin therapy, with the inclusion of a non-phenytoin Balinese group as a population reference comparator. The comparison with this reference group enabled evaluation of whether the observed CYP2C9 genotype distribution among phenytoin users represented a treatment-associated subgroup or reflected the underlying pharmacogenetic profile of the Balinese population. The main finding of this study is that CYP2C9*3 was substantially more frequent

Table 7. Distribution of CYP2C9 genotypes and CYP2C9 metabolizer phenotypes among study groups.

CYP2C9 Genotype / Metabolizer Phenotype	Phenytoin Users (n=100)	Non-Phenytoin Participants (n=100)	Total (N=200)
CYP2C9*3			
***1/*1 (Wild-type) / Extensive Metabolizer (EM)**	41 (41.0%)	36 (36.0%)	77 (38.5%)
***1/*3 (Heterozygous variant) / Intermediate Metabolizer (IM)**	42 (42.0%)	47 (47.0%)	89 (44.5%)
***3/*3 (Homozygous variant) / Poor Metabolizer (PM)**	17 (17.0%)	17 (17.0%)	34 (17.0%)
Total	100 (100%)	100 (100%)	200 (100%)

Table 8. Odds ratio values for CYP2C9 genotype and metabolizer phenotype in phenytoin users and non-phenytoin participants.

Variable	OR	95 % CI (Lower–Upper)
Genotype (Normal vs Variant)	1.235	0.698–2.186
Metabolizer phenotype (EM vs Non-EM)	1.235	0.698–2.186

than CYP2C9*2. Among phenytoin users, 59% of participants carried at least one CYP2C9*3 allele, consisting of 42% heterozygous *1/*3 genotypes classified as Intermediate Metabolizers and 17.0% homozygous *3/*3 genotypes classified as Poor Metabolizers based on the variant-specific categorization used in this study. In contrast, CYP2C9*2 was not found among phenytoin users and was detected in only one participant in the non-phenytoin group. This distribution indicates that CYP2C9*3 may be the more clinically relevant CYP2C9 decreased-function allele for pharmacogenetic consideration in this Balinese sample.

The predominance of CYP2C9*3 over CYP2C9*2 is consistent with broader pharmacogenomic evidence showing that CYP2C9 allele frequencies differ considerably across ethnic and geographic populations. Global pharmacogenomic analyses have demonstrated that CYP2C9*2 is more commonly reported in European, Middle Eastern, and several West Eurasian populations, whereas CYP2C9*3 tends to be more relevant in many Asian populations, although the magnitude of its frequency varies widely between subpopulations (Zhou et al., 2023; Biswas et al., 2025). This finding is particularly important because Indonesia is characterized by substantial ethnic and genetic diversity, and pharmacogenetic conclusions derived from one ethnic group cannot automatically be generalized to another. Available Indonesian data, although still limited, also suggest that CYP2C9*3 may be more informative than CYP2C9*2 in several local populations. For example, studies involving Papuan and Javanese-related samples reported low or absent CYP2C9*2 frequencies, while CYP2C9*3 appeared with more observable variation (Niruri et al., 2021; Tuba et al., 2021). Therefore, the present study highlights the importance of considering CYP2C9*3 in pharmacogenetic screening among the Balinese population, where CYP2C9*2 appears to be rare and CYP2C9*3 represents the predominant decreased-function allele identified in this study. Broader multicenter studies involving diverse Indonesian ethnic groups are still required before these findings can be generalized to the national population. Beyond genotype distribution, the observed CYP2C9*3 variants corresponded to predicted metabolizer categories among phenytoin users, consisting of 41% Extensive Metabolizers (EM), 42% Intermediate Metabolizers (IM), and 17% Poor Metabolizers (PM). This distribution suggests that CYP2C9*3 is a major contributor to predicted CYP2C9 metabolic variability in the studied Balinese population.

The comparison between phenytoin users and non-phenytoin participants showed no statistically significant difference in the distribution of CYP2C9*3 genotypes. This result is biologically plausible because CYP2C9 polymorphisms are inherited germline genetic characteristics and are not caused by phenytoin exposure. Therefore, the non-phenytoin group should be interpreted as a population reference comparator rather than as a conventional control group for drug-induced genetic change. In other words, the absence of a significant difference between groups does not weaken the importance of CYP2C9*3; instead, it suggests that the observed CYP2C9*3 distribution may reflect the background pharmacogenetic profile of the Balinese population included in this study. This interpretation is important because the study objective was not to prove that phenytoin use changes genotype distribution, but to determine the prevalence of CYP2C9 polymorphisms and the corresponding metabolic type distribution among Balinese participants, particularly those receiving phenytoin.

The high proportion of CYP2C9*3 carriers among phenytoin users has relevant clinical pharmacology implications. Phenytoin is a narrow therapeutic index antiseizure medication with nonlinear Michaelis–Menten pharmacokinetics. This means that small changes in dose, metabolic capacity, liver function,

Table 9. Allele frequencies and Hardy–Weinberg Equilibrium analysis of CYP2C9 polymorphisms.

Group	Gene	Reference Allele Frequency (p)	Variant Allele Frequency (q)	χ^2 calculated	χ^2 critical (df=1; α=0.05)	Interpretation
Phenytoin users	CYP2C9*2	1.000	0.000	0.000	3.841	HWE
Phenytoin users	CYP2C9*3	0.620	0.380	1.181	3.841	HWE
Non-phenytoin	CYP2C9*2	0.995	0.005	0.003	3.841	HWE
Non-phenytoin	CYP2C9*3	0.595	0.405	0.062	3.841	HWE

albumin binding, or drug interactions may produce disproportionate changes in plasma concentration. CYP2C9 is one of the major enzymes involved in phenytoin metabolism, and decreased-function variants can reduce metabolic clearance, thereby increasing systemic drug exposure. Participants with the *1/*3 genotype are expected to have reduced CYP2C9 enzymatic activity compared with wild-type participants, while those with the *3/*3 genotype may have markedly reduced metabolic capacity. Clinically, this condition may increase vulnerability to concentration-related adverse effects, including nystagmus, ataxia, dizziness, cognitive slowing, central nervous system depression, cerebellar dysfunction, and other toxicity manifestations, particularly when therapeutic drug monitoring is not routinely performed (Patocka et al., 2020; Chang et al., 2020; Karnes et al., 2021).

The Clinical Pharmacogenetics Implementation Consortium guideline has recommended genotype-informed interpretation of phenytoin therapy because CYP2C9 decreased-function alleles may require dose adjustment, enhanced clinical monitoring, or more cautious titration. However, genotype should not be interpreted as the only determinant of phenytoin response or toxicity. CYP2C9 genotype interacts with multiple clinical and biological factors, including age, hepatic function, serum albumin concentration, renal status, concomitant medications, nutritional status, inflammation, adherence, and seizure severity. In addition, HLA-B variants, particularly HLA-B*15:02 in several Asian populations, are more directly related to severe cutaneous adverse reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis, whereas CYP2C9 variants are more closely associated with altered metabolism and exposure-related toxicity risk (Karnes et al., 2021; De Bellis et al., 2025). Therefore, the high CYP2C9*3 frequency observed in this study should be interpreted as a pharmacokinetic risk signal rather than a complete predictor of clinical outcome.

The very low frequency of CYP2C9*2 also deserves specific interpretation. In the phenytoin group, all participants showed the *1/*1 genotype for CYP2C9*2, while only one heterozygous *1/*2 participant was identified in the non-phenytoin group. This pattern indicates that CYP2C9*2 contributes minimally to predicted CYP2C9 metabolic variability in this sample. From a statistical perspective, the rarity of CYP2C9*2 produces sparse genotype categories and zero-count cells, making conventional Chi-square testing inappropriate for full genotype comparison. From a clinical perspective, this finding suggests that routine pharmacogenetic evaluation in this population may obtain greater practical value from CYP2C9*3 assessment than from CYP2C9*2 assessment alone. However, CYP2C9*2 should not be completely disregarded because rare alleles may still be clinically important at the individual level, particularly when combined with other decreased-function variants or clinical risk factors.

For CYP2C9*3, the use of a 2 × 3 Chi-square test was appropriate because the genotype categories had adequate expected counts. The statistical result showed no significant difference between phenytoin users and non-phenytoin participants. This should be interpreted carefully. The test does not evaluate whether CYP2C9*3 influences phenytoin plasma concentration or adverse drug reactions; rather, it evaluates whether genotype distribution differs between the two study groups. Since both groups were ethnically Balinese and recruited from the same regional context, a similar distribution is expected. Therefore, the non-significant result supports the conclusion that the observed CYP2C9*3 distribution reflects the underlying genetic characteristics of the Balinese population rather than an effect of phenytoin exposure. A different study design would be required to evaluate associations between CYP2C9 genotype and clinical outcomes, such as phenytoin plasma concentration, dose-adjusted plasma concentration, or adverse drug reactions.

The distribution of CYP2C9*3 genotypes and the corresponding predicted metabolizer phenotype classification showed a similar pattern between phenytoin users and non-phenytoin participants, with no significant difference ($p = 0.739$). Intermediate Metabolizers (IM) were the most common category, followed by Extensive Metabolizers (EM), while Poor Metabolizers (PM) were the least common. Odds ratio analysis showed no significant association between phenytoin use and CYP2C9 genotype or predicted metabolizer phenotype status (OR = 1.235; 95% CI 0.698–2.186). These findings suggest that the observed CYP2C9*3 genotype distribution primarily reflects the underlying genetic variation of the Balinese population rather than phenytoin exposure.

These findings align with previous studies (Daly et al., 2018; Fekete et al., 2021) which stated that CYP2C9 variation is germline and not influenced by drugs or the environment. The similarity in genotype distribution in both groups indicates a relatively homogeneous CYP2C9 genetic profile in the Balinese population. Other studies also reported that the CYP2C9*2 and CYP2C9*3 alleles are more influenced by ethnic factors than external factors (Johnson et al., 2020; Caudle et al., 2022). Therefore, the non-significant OR results confirm that phenytoin use does not affect the genetic distribution of CYP2C9 but is only associated with interindividual variation in drug response.

The Hardy–Weinberg Equilibrium analysis provides additional support for interpreting the findings at the population level. For CYP2C9*3, the observed

genotype distribution in both phenytoin and non-phenytoin groups appeared consistent with expected Hardy–Weinberg proportions, suggesting that the distribution of this variant in the sampled population was not strongly distorted by major genotyping error, extreme selection, or sampling imbalance (Abramovs et al., 2020). This is relevant because pharmacogenetic prevalence studies rely on genotype distributions that reasonably reflect the population under investigation. For CYP2C9*2, however, interpretation of Hardy–Weinberg Equilibrium is limited by the extremely low minor allele count. When a variant is very rare, even a single heterozygous participant can influence frequency estimates, and statistical testing may have limited interpretability (Pratt et al., 2020). Thus, the HWE result for CYP2C9*2 should be viewed descriptively rather than as strong evidence of population equilibrium.

At the molecular level, the clinical relevance of CYP2C9*2 and CYP2C9*3 is related to their functional consequences on CYP2C9 enzyme activity. CYP2C9*2 corresponds to rs1799853, involving a C430T substitution that results in the Arg144Cys amino acid change, while CYP2C9*3 corresponds to rs1057910, involving an A1075C substitution that produces the Ile359Leu amino acid change. The CYP2C9*3 variant is generally associated with a more pronounced reduction in enzyme activity than CYP2C9*2, which helps explain why CYP2C9*3 is often considered highly relevant for drugs that depend substantially on CYP2C9 mediated metabolism, including phenytoin and warfarin (Yuan et al., 2023; Zhou et al., 2023; Karnes et al., 2021). In the present study, the relatively high proportion of *1/*3 and *3/*3 genotypes indicates that a considerable number of Balinese participants may have reduced metabolic capacity for CYP2C9 substrates. This does not necessarily mean that all carriers will experience toxicity, but it indicates a higher probability of altered exposure under certain clinical conditions.

The use of PCR-RFLP in this study provides a practical and accessible method for detecting targeted CYP2C9 variants in a local clinical research setting. The successful amplification of CYP2C9*2 and CYP2C9*3 fragments across all samples supports the technical feasibility of the method. RFLP patterns enabled genotype identification based on enzyme digestion fragments, with CYP2C9*2 and CYP2C9*3 genotypes differentiated by their expected band profiles. Nevertheless, PCR-RFLP has inherent limitations. Small fragments, such as the 29 bp fragment in CYP2C9*3 digestion, may be difficult to visualize clearly on standard agarose gel electrophoresis, and interpretation may depend on the visibility of the larger diagnostic fragments. Moreover, PCR-RFLP only detects predefined variants and cannot identify other CYP2C9 alleles, copy number variation, rare variants, or variants in other pharmacogenes. Therefore, while PCR-RFLP is suitable for focused screening, broader genotyping platforms or sequencing-based methods would be needed for more comprehensive pharmacogenetic profiling.

The findings of this study have potential implications for precision medicine implementation in Indonesian clinical settings. In hospitals where phenytoin remains widely used due to availability, cost, and clinical familiarity, identifying patients with decreased CYP2C9 metabolic capacity may support safer dose initiation, closer monitoring, and early recognition of toxicity. This is particularly relevant in settings where routine phenytoin therapeutic drug monitoring may not always be available or may be performed only after clinical problems occur. A targeted pharmacogenetic approach could help identify patients who may benefit from more conservative dosing strategies or alternative antiseizure medication selection. Nevertheless, implementation should be realistic and context-sensitive. CYP2C9 genotyping should not replace clinical judgment, but it can complement existing therapeutic monitoring and medication safety practices.

This study also contributes to the broader development of ethnicity-specific pharmacogenetic databases in Indonesia. The Balinese population has cultural, geographic, and ancestral characteristics that may differ from other Indonesian populations. Because pharmacogenetic allele frequencies vary substantially across populations, local evidence is necessary before designing national-level screening priorities. The high frequency of CYP2C9*3 observed in this study suggests that CYP2C9*3 may be a meaningful candidate marker in Balinese pharmacogenetic research and potentially in clinical screening programs involving CYP2C9 substrate drugs. However, wider multicenter studies involving larger samples and multiple Balinese subregions are needed to confirm the representativeness of this finding.

Despite its contribution, this study has several limitations. First, the genetic analysis was limited to CYP2C9*2 and CYP2C9*3 variants; therefore, other relevant pharmacogenes, such as CYP2C19 and HLA-B*15:02, were not evaluated. Second, predicted metabolizer status was classified based on the analyzed CYP2C9 genotype categories and may not fully represent the overall genetic variability affecting phenytoin metabolism. Third, clinical factors that may influence phenytoin response, including dosage, plasma concentration, serum albumin, liver function, adherence, drug interactions, and adverse drug reactions, were not assessed. Finally, the non-phenytoin group served only as a population comparator for genotype distribution and should not be considered a clinical control group for treatment response.

Future studies should integrate broader pharmacogenetic panels, therapeutic drug monitoring, and prospective clinical outcome assessment. A stronger

design would include baseline genotype determination, standardized phenytoin dose documentation, serial plasma concentration measurement, structured adverse event monitoring, seizure outcome classification, and adjustment for clinical covariates such as age, liver function, albumin level, concomitant drugs, and adherence. Incorporating HLA-B genotyping would also be valuable for evaluating severe cutaneous adverse reaction risk, especially in Asian populations. Such an approach would allow researchers to move beyond prevalence estimation toward clinically actionable pharmacogenetic modeling.

Overall, this study demonstrates that CYP2C9*3 is considerably more prevalent than CYP2C9*2 in the Balinese participants studied, including those using phenytoin. The similar genotype distribution between phenytoin users and non-phenytoin participants indicates that this pattern likely reflects the background genetic profile of the sampled Balinese population rather than an effect of phenytoin exposure. Clinically, the high proportion of predicted Intermediate and Poor Metabolizers based on CYP2C9*3 suggests a potential need for greater attention to genotype-informed phenytoin therapy, especially in patients at risk of concentration-related toxicity. These findings support the importance of developing local pharmacogenetic evidence as a foundation for safer, more individualized antiseizure medication therapy in Indonesia.

5. CONCLUSION

Among Balinese participants receiving phenytoin therapy, the CYP2C9*2 polymorphism was not detected, whereas CYP2C9*3 demonstrated greater genetic variation, with predicted metabolizer phenotype distributions of 41% Extensive Metabolizers (EM), 42% Intermediate Metabolizers (IM), and 17% Poor Metabolizers (PM). Comparison with the non-phenytoin reference group showed no significant difference in CYP2C9*3 genotype distribution or predicted metabolizer phenotype classification ($p = 0.739$). These findings suggest that the observed CYP2C9*3 distribution likely reflects the underlying genetic variation of the Balinese population rather than an effect of phenytoin use. This study provides pharmacogenetic baseline data on CYP2C9 distribution and predicted metabolizer phenotype variability, which may support future investigations evaluating phenytoin plasma concentrations and therapeutic response in the Balinese population.

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Author contribution

All authors contributed substantially to the study conception, design, data acquisition, data analysis, interpretation of findings, manuscript drafting, and critical revision. All authors approved the final manuscript and agreed to be accountable for the integrity and accuracy of the work.

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Conflict of interest

The author declares no conflict of interest related to this study.

Ethical approval

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