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Original Article

CALU rs1043550 polymorphism and stable acenocoumarol maintenance-dose requirements in Algerian patients: an exploratory pharmacogenetic study

Polymorphisme CALU rs1043550 et besoins en dose d'entretien stable d'acénocoumarol chez des patients algériens : étude pharmacogénétique exploratoire

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ABSTRACT

Background and objective: Acenocoumarol maintenance-dose requirements show substantial interindividual variability, and the contribution of CALU rs1043550 (A>G) remains uncertain, particularly in North African populations. This study aimed to assess the association between CALU rs1043550 and stable acenocoumarol maintenance dose in Algerian patients after adjustment for clinical factors and VKORC1 rs9923231. Materials and Methods: This exploratory secondary analysis included 80 of 119 participants with available CALU genotypes from a prospective single-centre cohort. Stable daily dose was log10-transformed and evaluated using an additive CALU G-allele model adjusted for age, sex, weight, amiodarone, INR target, and categorical VKORC1 rs9923231. A sensitivity model additionally adjusted for CYP2C9*2 (rs1799853) and CYP2C9*3 (rs1057910). Results: CALU genotypes were AA in 53 patients (66.3%), AG in 22 (27.5%), and GG in 5 (6.3%); genotypes were unavailable for 39/119 patients (32.8%). Mean stable doses were 3.16±1.74, 3.46±2.23, and 2.61±0.96 mg/day, respectively (unadjusted P=0.622). The primary adjusted dose ratio per G allele was 1.03 (95% CI 0.89–1.19; P=0.669); with additional adjustment for CYP2C9*2 and *3, it was 1.03 (95% CI 0.89–1.19; P=0.725). Conclusion: No statistically significant association was detected in this exploratory cohort, including after additional adjustment for CYP2C9 variants. The limited sample, particularly five GG homozygotes, missing CALU genotypes, and unmeasured dietary vitamin K preclude definitive clinical conclusions.

Keywords: acenocoumarol; CALU; calumenin; rs1043550; pharmacogenetics

RESUME

Introduction et objectif La dose d'entretien d'acénocoumarol varie fortement d'un patient à l'autre. L'effet du polymorphisme CALU rs1043550 (A>G) demeure mal établi en Afrique du Nord. Cette étude visait à évaluer son association avec la dose d'entretien stable chez des patients algériens, après ajustement sur des facteurs cliniques et VKORC1 rs9923231. Matériels et méthodes : Cette analyse secondaire exploratoire a inclus 80 des 119 participants d'une cohorte prospective monocentrique, pour lesquels le génotype CALU était disponible. La dose quotidienne stable, transformée en log10, a été étudiée selon un modèle additif ajusté sur l'âge, le sexe, le poids, l'amiodarone, la cible d'INR et le génotype catégoriel VKORC1 rs9923231. Une analyse de sensibilité a également pris en compte CYP2C9*2 (rs1799853) et CYP2C9*3 (rs1057910). Résultats : Les génotypes CALU étaient AA chez 53 patients (66,3 %), AG chez 22 (27,5 %) et GG chez 5 (6,3 %) ; le génotype était indisponible chez 39/119 patients (32,8 %). Les doses moyennes étaient respectivement de 3,16±1,74, 3,46±2,23 et 2,61±0,96

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mg/j (P non ajusté=0,622). Le ratio de dose ajusté par allèle G était de 1,03 (IC à 95 % 0,89–1,19 ; P=0,669) dans le modèle principal, puis de 1,03 (IC à 95 % 0,89–1,19 ; P=0,725) après ajustement supplémentaire sur CYP2C9. Conclusion : Aucune association statistiquement significative n'a été détectée, y compris après prise en compte de CYP2C9. Les faibles effectifs, notamment les cinq homozygotes GG, les génotypes CALU manquants et l'absence de mesure de la vitamine K alimentaire limitent la portée des conclusions.

Mots clés : acénocoumarol ; CALU ; caluménine ; rs1043550 ; pharmacogénétique

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Received on: 13/10/2026
Revised on: 02/11/2026
Accepted on: 09/11/2026

Introduction

Vitamin K antagonists remain important anticoagulants in clinical situations in which direct oral anticoagulants are unsuitable or contraindicated. Acenocoumarol has a narrow therapeutic index and marked interindividual variability in dose requirements, making stable-dose identification dependent on both clinical and genetic determinants [1].

Calumenin, encoded by CALU, is an endoplasmic-reticulum calcium-binding protein involved in the vitamin K-dependent gamma-carboxylation system. Experimental work has shown that calumenin can interact with and inhibit components of the vitamin K cycle, providing a biologically plausible link between CALU variation and coumarin sensitivity [2,3]. The 3' untranslated-region polymorphism CALU rs1043550, historically described as A29809G, has therefore attracted interest as a potential modifier of oral-anticoagulant dose.

Human pharmacogenetic findings have been inconsistent. In a Spanish acenocoumarol cohort, rs1043550 appeared to enhance the effect of VKORC1 c.1173C>T rather than exert a large independent effect [4]. Other work examining acenocoumarol and phenprocoumon found that established VKORC1 and CYP2C9 variants dominated dose variability, with limited contribution from CALU [5]. A later warfarin study found no significant independent contribution of rs1043550 [6]. Studies in Egyptian patients have also suggested population-specific CALU signals, although some evaluated other CALU variants or warfarin rather than acenocoumarol [7,8].

North African data on CALU rs1043550 and acenocoumarol remain limited. The underlying Algerian cohort has previously been used to evaluate VKORC1 genotype-dose associations and, separately, the transportability of published acenocoumarol dosing equations; CALU rs1043550 was not analysed in either publication [9,10]. We therefore conducted an exploratory secondary analysis to examine the association between CALU rs1043550 and stable acenocoumarol maintenance dose among Algerian patients with available CALU genotypes, with an additional assessment of the robustness of the CALU estimate after adjustment for CYP2C9*2 and CYP2C9*3.

Material and Methods

Study design, setting, and relationship to previous reports

This was a targeted secondary pharmacogenetic analysis of a prospective, single-centre observational cohort recruited in the Department of Cardiology of the University Hospital Centre of Sétif, Algeria, between November 2017 and September 2019. The cohort design, follow-up procedures, stable-dose ascertainment, and previously analysed VKORC1 variants have been reported elsewhere [9]. A separate study used the same underlying cohort to externally validate published acenocoumarol dose-prediction equations [10]. The present analysis addresses a distinct question focused on CALU rs1043550, which was not analysed in either published article.

The study protocol was approved by the Institutional Ethics Committee of CHU Constantine, Algeria (EC/CHUC/09/05-2017; 10 May 2017). All participants provided written informed consent before enrolment. The original consent authorised storage of DNA and its subsequent use in related pharmacogenetic investigations. Analyses used deidentified study identifiers.

Participants and stable-dose outcome

Adults aged 18 years or older were eligible if they had received acenocoumarol for at least 6 months, were followed at CHU Sétif, and met prespecified criteria for stable anticoagulation. Stability required an indication-specific INR within the therapeutic range over at least 3 months and time in therapeutic range >60%, estimated using the Rosendaal method [11]. Stable maintenance dose was defined as the arithmetic mean of the prescribed daily doses recorded at visits during which INR remained within the indication-specific therapeutic range. The final locked cohort comprised 119 participants; CALU genotype data were available for 80 (67.2%) and unavailable for 39 (32.8%). The reasons for genotype unavailability could not be established from the final analytical records. No imputation of

missing CALU genotypes was performed.

DNA extraction and CALU rs1043550 genotyping

Genomic DNA was extracted from EDTA-anticoagulated peripheral blood using a salting-out procedure and quantified by spectrophotometry. CALU rs1043550 (A29809G; A>G) was genotyped by PCR-RFLP using a laboratory-optimised protocol based on the method of González-Conejero et al. [4]. The forward primer was 5'-GGATGGCAAGCTTACCAAGG-3' and the reverse primer was 5'-GTTTGTAGTAACAGTCTCAG-3'. PCR was performed in a final volume of 25 µL containing 100 ng genomic DNA, 1× buffer, 1.7 mmol/L MgCl2, 0.2 mmol/L dNTPs, 0.4 µmol/L of each primer, and 1 U Taq DNA polymerase. Cycling conditions were 95°C for 5 min, followed by 35 cycles of 95°C for 30 s, 60°C for 30 s, and 72°C for 3 min, with a final extension at 72°C for 5 min. The expected amplicon size was 203 bp.

A 5-µL aliquot of PCR product was digested overnight at 37°C with 2 U of SatI in a final volume of 10 µL containing 1× digestion buffer. Digested fragments were separated on 2% agarose gel and visualised under ultraviolet illumination. Expected fragment patterns were 148 and 55 bp for AA, 148, 95, 55 and 53 bp for AG, and 95, 55 and 53 bp for GG. Genotype frequencies were assessed for Hardy-Weinberg equilibrium using an exact test [12].

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median with interquartile range, as appropriate, and categorical variables as counts and percentages. Characteristics of participants with available and unavailable CALU genotypes were compared using Welch's t test for continuous variables and chi-square tests for categorical variables. Stable daily acenocoumarol dose was right-skewed and was log10-transformed for regression analyses.

The primary genetic model treated rs1043550 as an additive G-allele count (AA=0, AG=1, GG=2). The prespecified adjusted linear regression model included age (years), sex, body weight, amiodarone use, target INR category, and categorical VKORC1 rs9923231 genotype because rs9923231 had previously shown a non-additive association with dose in this cohort [9]. To address the potential confounding effect of CYP2C9, a post-review sensitivity model additionally included CYP2C9*2 (rs1799853; number of T alleles, 0–2) and CYP2C9*3 (rs1057910; number of C alleles, 0–2) as separate additive covariates. CYP2C9 genotype calls were available for all 80 CALU-genotyped participants. These two CYP2C9 variants were analysed as separate allele counts; haplotype phase was not inferred. Habitual dietary vitamin K intake was not quantified and was not included in either model. Stable daily dose was log10-transformed; regression coefficients were back-transformed as 10^β and reported as dose ratios with 95% confidence intervals. Secondary CALU analyses used categorical genotype, dominant (AG+GG vs AA), and recessive (GG vs AA+AG) models. Overall categorical CALU effects were assessed by a two-degree-of-freedom partial F test and departure from the additive assumption was assessed by comparing nested models. The single verified 12 mg/day observation was excluded in an additional sensitivity analysis. Residual normality, heteroscedasticity (Breusch-Pagan test), and variance inflation factors were evaluated. Two-sided P<0.05 was considered statistically significant. In light of the small exploratory subset, non-significant findings were not interpreted as evidence of equivalence or absence of an effect. Reporting was checked against STREGA recommendations [13].

Results

CALU-genotyped subset

CALU rs1043550 genotypes were available for 80 (67.2%) of the 119 participants; 39 (32.8%) had no available CALU genotype. The genotyped subset had a mean age of 53.94±14.67 years, 45 participants (56.3%) were women, and the mean stable acenocoumarol dose was 3.21±1.84 mg/day. Venous thromboembolism was the most frequent indication (48/80, 60.0%). Fourteen participants (17.5%) received amiodarone and 17 (21.3%) had a target INR category of 3-4. No statistically significant differences were detected between participants with available and unavailable CALU genotypes in age, sex, body weight, BMI, stable dose, target INR category, amiodarone use, treatment indication, or VKORC1 rs9923231 distribution (all P>0.05; Table 1). These comparisons do not establish that genotype availability was unrelated to unmeasured characteristics.

Table 1. Comparison of participants with available and unavailable CALU rs1043550 genotypes.

Characteristic	CALU available (n=80)	CALU unavailable (n=39)	P value
Age, years	53.94±14.67	52.92±18.31	0.764
Female sex	45 (56.3%)	24 (61.5%)	0.726
Body weight, kg	74.03±14.12	76.18±17.64	0.508
BMI, kg/m²	27.20±5.24	28.18±7.88	0.487
Stable dose, mg/day	3.21±1.84	2.81±0.88	0.112
Venous thromboembolism	48 (60.0%)	24 (61.5%)	0.806*
Target INR 3-4	17 (21.3%)	7 (17.9%)	0.859
Amiodarone use	14 (17.5%)	8 (20.5%)	0.884
VKORC1 rs9923231: GG / GA / AA	10 / 42 / 28	5 / 21 / 13	0.984

Values are mean ± SD or n (%). *P value refers to the overall three-category indication distribution. BMI, body mass index; INR, international normalised ratio.

CALU genotype distribution and unadjusted dose

The rs1043550 genotype distribution was AA in 53 participants (66.3%), AG in 22 (27.5%), and GG in 5 (6.3%). The G-allele frequency was 20.0%, and the distribution was compatible with Hardy-Weinberg equilibrium (exact P=0.286). Mean stable doses were 3.16±1.74 mg/day in AA carriers, 3.46±2.23 mg/day in AG carriers, and 2.61±0.96 mg/day in GG carriers. There was no evidence of an unadjusted difference in mean dose across the three genotypes (P=0.622; Table 2 and Fig. 1). Representative PCR-RFLP banding patterns of the three CALU genotypes after SatI digestion are shown in Fig. 2.

Table 2. CALU rs1043550 genotype distribution and stable acenocoumarol dose.

Genotype	n (%)	Mean±SD dose, mg/day	Median (IQR), mg/day
AA	53 (66.3%)	3.16±1.74	3.00 (2.00-4.00)
AG	22 (27.5%)	3.46±2.23	3.00 (2.00-3.88)
GG	5 (6.3%)	2.61±0.96	2.57 (2.00-3.00)

G-allele frequency=20.0%; exact Hardy-Weinberg P=0.286; unadjusted one-way ANOVA P=0.622.

Adjusted association analyses

In the prespecified adjusted additive model, no statistically significant association was detected between CALU rs1043550 G-allele count and stable maintenance dose after adjustment for the specified clinical covariates and VKORC1 rs9923231. The adjusted dose ratio per G allele was 1.03 (95% CI 0.89–1.19; P=0.669). The unrestricted categorical model likewise showed no statistically significant overall association (P=0.614): relative to AA, the adjusted dose ratio was 1.09 (95% CI 0.90–1.33; P=0.360) for AG and 0.96 (95% CI 0.67–1.38; P=0.828) for GG. There was no evidence that the additive specification was inadequate (lack-of-fit P=0.375). Dominant and recessive models were also non-significant (Table 3). Given the very small GG subgroup, genotype-specific estimates are imprecise.

Table 3. Adjusted association of CALU rs1043550 with stable acenocoumarol maintenance dose.

Genetic model	Comparison	Adjusted dose ratio	95% CI	P value	Overall P
Additive	Per G allele	1.03	0.89-1.19	0.669	—
Categorical	AG vs AA	1.09	0.90-1.33	0.360	0.614
Categorical	GG vs AA	0.96	0.67-1.38	0.828	0.614
Dominant	AG+GG vs AA	1.07	0.89-1.28	0.467	—
Recessive	GG vs AA+AG	0.94	0.65-1.34	0.717	—

Models used log10-transformed stable dose and were adjusted for age, sex, body weight, amiodarone use, target INR category, and categorical VKORC1 rs9923231 genotype. Dose ratios are 10^β. CI, confidence interval.

Additional CYP2C9-adjusted sensitivity analysis. CYP2C9*2 and CYP2C9*3 genotypes were available in all 80 participants with CALU genotypes. CYP2C9*2 genotypes were CC in 43, CT in 34 and TT in 3 participants; CYP2C9*3 genotypes were AA in 53, AC in 22 and CC in 5 participants. Adding the two CYP2C9 allele counts to the original model yielded a CALU dose ratio per G allele of 1.03 (95% CI 0.89–1.19; P=0.725), essentially unchanged from the primary estimate (Table 4). The joint addition of CYP2C9*2 and CYP2C9*3 did not improve model fit significantly (partial F test P=0.669), although this comparison was underpowered and does not negate the known pharmacological relevance of CYP2C9. The CYP2C9-adjusted categorical CALU model had an overall P=0.701; dominant and recessive models were also non-significant. Excluding the single 12 mg/day observation from the CYP2C9-adjusted additive model yielded a similar CALU dose ratio of 1.04 (95% CI 0.90–1.20; P=0.616).

Table 4. Sensitivity regression model additionally adjusted for CYP2C9*2 and CYP2C9*3 (n=80).

Predictor	Ratio (95% CI)	P
CALU / G allele	1.03 (0.89–1.19)	0.725
CYP2C9*2 / T	0.94 (0.81–1.10)	0.443
CYP2C9*3 / C	1.03 (0.88–1.20)	0.741

Outcome: log10 stable daily acenocoumarol dose. Model included age, sex, body weight, amiodarone use, target INR category, categorical VKORC1 rs9923231 genotype, and the two displayed CYP2C9 allele-count terms, in addition to CALU. Ratios = 10^β; CI, confidence interval. This is a post-review sensitivity analysis; the original prespecified model remains the primary analysis.

Diagnostics of the CYP2C9-adjusted sensitivity model did not reveal marked assumption violations (Shapiro-Wilk P=0.390; Breusch-Pagan P=0.714; all variance inflation factors <3). For comparison, diagnostics of the original model were similar (Shapiro-Wilk P=0.296; Breusch-Pagan P=0.724; all variance inflation factors <3). Excluding the single participant receiving 12 mg/day from the original model yielded a per-G-allele ratio of 1.04 (95% CI 0.90–1.19; P=0.589).

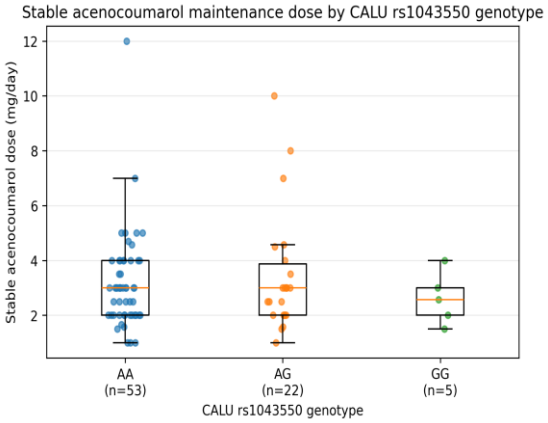


Figure 1. Stable acenocoumarol maintenance dose according to CALU rs1043550 genotype. Boxes show the interquartile range with the median; points represent individual participants.

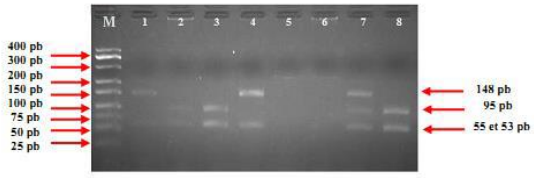


Figure 2. Representative agarose gel electrophoresis of SatI-digested PCR products for the CALUrs1043550 (29809A>G) polymorphism. M, 25-bp DNA ladder; lanes 1 and 4, AA genotype (expected fragments: 148 and 55 bp); lanes 2, 3 and 8, GG genotype (95, 55 and 53 bp); lane 7, AG genotype (148, 95, 55 and 53 bp). The 53-bp and 55-bp fragments are not individually resolved under these conditions.

Discussion

In this exploratory secondary analysis, no statistically significant association between CALU rs1043550 and stable acenocoumarol maintenance dose was detected after adjustment for selected clinical covariates and VKORC1 rs9923231. The G-allele frequency was 20.0% and the adjusted CALU per-allele dose ratio was close to 1. Importantly, additional adjustment for CYP2C9*2 and CYP2C9*3 in a sensitivity model produced a very similar estimate (1.03; 95% CI 0.89–1.19; P=0.725). These results do not establish absence of a CALU effect, particularly in a small sample with only five GG homozygotes.

These findings are compatible with the view that rs1043550 is not a major stand-alone determinant of acenocoumarol dose. González-Conejero et al. originally reported that the CALU A29809G variant could modify the anticoagulant response, but their most notable observation was an interaction with VKORC1 c.1173C>T rather than a large isolated CALU effect [4]. In another study of acenocoumarol and phenprocoumon, Cadamuro et al. found that VKORC1 and CYP2C9 were the dominant determinants of maintenance dose and that CALU contributed only minor additional information [5]. In a larger warfarin cohort, Glurich et al. similarly found no significant independent contribution of rs1043550 [6].

Differences among published studies may reflect anticoagulant choice, ancestry, allele frequencies, treatment indications, clinical covariates, and the genetic background in which CALU is evaluated. Egyptian warfarin studies have reported CALU-related signals, but these findings are not directly comparable because some examined a different CALU variant, rs339097, or used warfarin rather than acenocoumarol [7,8]. In the present small, incompletely genotyped subset, failure to detect a statistically significant association is not sufficient to rule out a modest, genotype-specific, or context-dependent effect of rs1043550.

The biological rationale for CALU remains plausible. Calumenin can inhibit the vitamin K-dependent gamma-carboxylation system and has been implicated experimentally in resistance to coumarin anticoagulants [2,3]. rs1043550 lies in the 3' untranslated region and may mark regulatory variation rather than directly alter protein structure [4]. If its clinical effect depends on other vitamin K-cycle variants, a modest marginal association may be difficult to detect in small cohorts. This is particularly relevant here because only five participants were GG homozygotes.

This analysis has several strengths. The clinical endpoint was a prospectively ascertained stable maintenance dose; CALU was assessed under several inheritance models; and the primary model accounted for relevant clinical factors and the previously described non-additive VKORC1 rs9923231 association. The availability of CYP2C9*2 and CYP2C9*3 genotypes for all 80 CALU-genotyped participants enabled a directly comparable additional sensitivity analysis, whose result was consistent with the primary estimate. Excluding the single high-dose observation did not materially change the estimate. Although measured baseline characteristics did not differ significantly by CALU-genotyping status, this does not exclude selection bias associated with unmeasured factors.

Important limitations warrant emphasis. CALU genotypes were available for only 80 of 119 participants, leaving 39 (32.8%) without genotype data. The reasons for unavailability could not be

reconstructed from the available analytical records, and the absence of statistically significant measured baseline differences does not establish that the missingness was random. The small sample and particularly the five GG homozygotes limit precision and statistical power to detect modest or genotype-specific associations. Although the additional model accounted for CYP2C9*2 and CYP2C9*3, this exploratory analysis cannot exclude residual confounding from other genetic variants or clinical factors, and these SNPs were included as unphased allele counts rather than inferred diplotypes. Habitual dietary vitamin K intake was not quantified, so its influence on dose variation or on the observed CALU estimate cannot be assessed. Evidence regarding dietary vitamin K and anticoagulation control is heterogeneous [15]. Genotyping relied on PCR-RFLP without independent sequencing confirmation in the available analytical records. The single-centre stable-treatment cohort should not be extrapolated to treatment initiation or to the wider North African population. The underlying cohort has been reported previously, but the CALU rs1043550 question was not evaluated in those articles [9,10]. Overall, the findings remain preliminary and hypothesis-generating.

Current cardiovascular pharmacogenomics emphasizes the importance of evaluating genotype effects and dosing models in their intended populations and clinical settings [14]. Larger, multicentre North African studies should seek to obtain complete CALU genotyping, systematically document reasons for missing samples, verify variant calls independently, incorporate CYP2C9 and other established pharmacogenetic factors, quantify habitual dietary vitamin K intake, and plan adequate sample sizes for detecting modest genetic effects and interactions.

Conclusion

In this exploratory subset of 80 stable acenocoumarol-treated Algerian patients, no statistically significant association between CALU rs1043550 and maintenance dose was detected in the main adjusted model or in a sensitivity model additionally adjusting for CYP2C9*2 and CYP2C9*3. These findings cannot establish that CALU rs1043550 lacks a clinical effect, given the very small GG group, the 32.8% of patients without CALU genotypes, and the absence of quantified dietary vitamin K intake. Replication in larger, comprehensively genotyped and clinically characterised North African cohorts is needed.

Conflicts of interest

The authors declare no conflicts of interest.

Funding

None

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