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Association of *EPHX1* Gene Polymorphisms (rs1051740 and rs2234922) with Preeclampsia among Pregnant Women in Lagos, Nigeria: A Molecular Case-Control Study

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ABSTRACT

Background: Preeclampsia (PE) remains a contributor to maternal and foetal morbidity and mortality, especially in resource-limited regions. Genetic predisposition may influence susceptibility, with the *EPHX1* gene, central to xenobiotic metabolism and oxidative stress, implicated through two missense single nucleotide polymorphisms (SNPs), rs1051740 and rs2234922. Study determined the association between *EPHX1* SNPs and preeclampsia risk, evaluating allele frequencies and clinical correlations**.**

Methodology: A case-control study conducted among 200 pregnant women (97 with PE and 103 controls) across three maternity hospitals in Lagos State. Ethical approvals and informed consent were obtained. Data on socio-demographic, lifestyle, and maternal clinical parameters were collected using structured questionnaires. Blood samples were collected for *EPHX1* SNPs genotyped using PCR-based method. Descriptive statistics, chi-square and Fisher's exact tests, t-tests, correlation, and linear regression were conducted with $p < 0.05$.

Results: The mean age of women with preeclampsia was higher than that of normotensive women but no significant age difference was observed between the two groups (PE: 31.93 ± 4.91; Controls: 30.55 ± 5.73; $p = 0.071$). Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and proteinuria were all significantly elevated in the preeclamptic group compared to controls ($p < 0.0001$). The rs1051740 C allele (mutant, minor) was significantly more frequent and associated with PE cases (49.5%) than controls (15.8%) ($p = 7.4 \times 10^{-7}$), showing a positive correlation with SBP ($r = 0.222$, $p = 0.030$). While the rs2234922 A allele (wild-type, major) was also significantly associated with PE ($p = 0.00784$), it did not exhibit a statistically significant correlation with SBP. Both alleles confer PE risk.

Conclusion: Findings highlight a significant association between *EPHX1* SNPs and preeclampsia, emphasising the role of genetic predisposition within the multifactorial context of disease risk in this population

Keywords: allele frequency, *EPHX1,* preeclampsia, polymerase chain reaction (PCR)-based genotyping, single nucleotide polymorphisms

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INTRODUCTION

Preeclampsia (PE) is a serious hypertensive disorder of pregnancy with multifactorial origins and systemic implications, primarily associated with placental dysfunction.[1] Clinically, preeclampsia is defined as new-onset hypertension (≥140/90 mmHg) after 20 weeks of gestation, with or without proteinuria (≥300 mg/24 h, protein:creatinine ratio ≥0.3 mg/mmol, or dipstick ≥1+ if quantitative methods are unavailable).[2] In the absence of proteinuria, diagnosis relies on evidence of maternal end-organ dysfunction affecting the renal, hepatic, neurological, or haematological systems.[2,3] Foetal complications include growth restriction, oligohydramnios, and increased perinatal mortality.[4,5] Despite well-established diagnostic criteria, the underlying aetiology remains incompletely understood, with oxidative stress and genetic predisposition implicated as central mechanisms.[6]

Globally, PE affects 2–8% of pregnancies and accounts for approximately 46,000 maternal and 500,000 foetal or neonatal deaths annually, as previously reported by the World Health Organization (WHO). Subsequent data (2025) indicate a prevalence of 3–8%, with hypertensive disorders of pregnancy responsible for 16% of maternal deaths worldwide, equivalent to 42,000 deaths in 2023.[7] Incidence is nearly seven times higher in developing regions, disproportionately affecting women in sub-Saharan Africa, South Asia, and Latin America.[8,9]

In Nigeria, a systematic review by Kokori et al.[10] reported a pooled prevalence of 4.51% for PE and 1.39% for eclampsia, with maternal and foetal mortality rates of 6.04% and 16.73%, respectively. Complications such as acute kidney injury, stroke, and aspiration pneumonia further highlight the burden of hypertensive disorders in this context. Without timely intervention, PE may progress to eclampsia, pulmonary oedema, hepatic rupture, HELLP syndrome, multi-organ failure, and placental abruption.[11] Delivery is the definitive treatment, as resolution occurs following placental removal. Risk factors include reproductive determinants (nulliparity, multiple gestation, advanced maternal age), chronic hypertension (including superimposed pre-eclampsia), obesity, family history, inadequate antenatal care, low socio-economic status, race/ethnicity, and lifestyle habits.[12,13]

Pathophysiologically, PE develops in two stages.[1,14] Stage 1 (placental phase) occurs early in pregnancy and is characterised by abnormal placental development and impaired spiral artery remodelling. Stage 2 (maternal phase) manifests after 20 weeks with hypertension and systemic involvement. Beyond these stages, PE is classified by onset (<34 weeks early; ≥34 weeks late), severity (mild or severe), and gestational age at delivery (<37 weeks preterm; ≥37 weeks term).[15,16] Underlying these clinical manifestations, increased placental metabolic activity elevates reactive oxygen species (ROS), which normally regulate trophoblast migration and angiogenesis.[17] In PE, excess ROS impair these processes, driving endothelial dysfunction and disease progression.

Genetic susceptibility to PE has been widely studied. Evidence indicates a complex interplay of maternal, paternal, and foetal genes rather than single-gene inheritance, although the precise mode remains undefined.[18,19] Non-Mendelian mechanisms, including epigenetics, genomic imprinting, and mitochondrial inheritance, may also contribute alongside environmental influences.[20-22] Familial clustering is well documented: daughters of affected mothers have a 20–40% increased risk, while twin studies estimate heritability involving both maternal and foetal genes (22–55%). Discordance among monozygotic twins further highlights the influence of foetal genetics and environmental factors.[21-25] Paternal contribution is also recognised, supporting the genetic conflict hypothesis, whereby paternal genes may elevate maternal blood pressure to enhance nutrient transfer, countered by maternal regulatory mechanisms.[20,26] Despite growing genetic research, African populations remain under-represented in genomic studies, comprising only 2.4% of entries in the GWAS catalogue while accounting for 7% of reported trait associations,[21,27] thereby limiting the generalisation of genetic association findings for African populations. This disparity underscores a persistent gap in genomic representation and emphasises the necessity to investigate genetic variants associated with disease susceptibility in under-represented populations.

The *EPHX1* (microsomal epoxide hydrolase 1) gene, involved in detoxification and antioxidant defence, has been implicated in preeclampsia (PE), hypercholanemia, and conditions such as foetal hydantoin syndrome and diphenylhydantoin toxicity.[28-31] Located on chromosome 1q42.12, the gene spans ~35 kb and comprises nine exons and eight introns.[32,33] Two functionally significant missense SNPs in *EPHX1* have been widely studied: rs1051740 (T>C; Tyr113His, exon 3, nucleotide 337) and rs2234922 (A>G; His139Arg, exon 4, nucleotide 416). The former reduces enzymatic activity by ~39%, potentially impairing detoxification of

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reactive epoxides and increasing oxidative stress, whereas the latter increases enzymatic activity by ~25%, which may alter cellular oxidative balance.[32,34]

This study investigates the association of *EPHX1* SNPs with preeclampsia among pregnant women in Lagos, Nigeria, comparing clinical, socio-demographic, and lifestyle characteristics, analysing allele frequencies, and examining correlations with clinical parameters. It aims to enhance understanding of the molecular basis of PE and identify genetic risk factors that may inform future risk stratification and targeted intervention.

MATERIALS AND METHODS

Study Design: This study employed a molecular case-control design to evaluate the association between SNPs in the *EPHX1* gene and the risk of PE among pregnant women in Lagos State, Nigeria. Given the relatively low prevalence of PE, this design provided an efficient framework for identifying cases and examining genetic associations. The five-month study period (August–December 2024) encompassed participant recruitment, questionnaire administration, and blood sample collection during routine antenatal visits.

Ethical Considerations: Ethical approvals were obtained from the Health Research Ethics Committee of the College of Medicine, University of Lagos (CMUL/HREC/05/24/1479), and the Lagos State Health Service Commission (LSHSC/2222/VOLV/110). All procedures involving human participants were conducted in accordance with institutional ethical standards and with the Declaration of Helsinki (2024 revision). Written informed consent was obtained from all participants.

Study Population: Participants were selected from three public healthcare facilities: Lagos University Teaching Hospital, Lagos Island Maternity Hospital, and Ikorodu General Hospital. These centres were chosen for their large and diverse antenatal populations. Eligible participants were women in their second trimester (≥20 weeks) who provided written informed consent. Cases were clinically diagnosed with preeclampsia, defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, with or without proteinuria of at least +1 on dipstick testing, or a personal/family history of hypertension or preeclampsia. Controls were normotensive pregnant women (BP <140/90 mmHg) without proteinuria, except for negligible trace findings not meeting diagnostic criteria. Exclusion criteria included multiple gestation, autoimmune disorders, prior antihypertensive therapy, first-trimester or near-term pregnancies, and chronic viral infection. Participants were enrolled through purposive sampling during routine antenatal visits.

Sample Size Determination: A total of 200 pregnant women were included (97 preeclampsia cases and 103 controls). Formal power calculations were not performed; however, the sample size was guided by principles commonly applied in genetic association studies, considering minor allele frequency (MAF), assumed effect size (odds ratio), significance level ($\alpha = 0.05$), and statistical power ($1 - \beta = 0.80$).[35] Genetic effects in complex diseases such as preeclampsia are typically modest (odds ratios 1.1–1.5), contributing ~0.05% to the variance of continuous traits.[36] Most studies are adequately powered to detect common variants (MAF >5%), while uncommon (1–5%) and rare (<1%) variants are more difficult to capture. The chosen sample size was considered sufficient to detect moderate to large associations, with allowance for missing data or genotyping errors.

Clinical Evaluation and Molecular Analysis: Participant data were collected using the structured Preeclampsia Phenotype Questionnaire (**PPQ**), a research instrument designed by Fagbayi et al. .[37] The **PPQ** consists of 27 items across three sections: maternal parameters (age, ethnicity, occupation, height, and weight), lifestyle factors (smoking and alcohol use), and maternal clinical parameters (including blood pressure and proteinuria), along with consent for blood sample collection. The questionnaire was pretested for clarity and cultural appropriateness in Nigeria during its initial validation by Fagbayi et al. [37], and was subsequently adopted for this study.

Five millilitres (5 mL) of whole blood were collected from study participants via venepuncture, transferred into EDTA Vacutainer tubes, and stored at −23°C until analysis. Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany) according to the manufacturer's protocol. DNA purity and concentration were assessed with a NanoDrop spectrophotometer.

Primer sequences for rs1051740 (F: 5'-GATCGATAAGTTCCGTTTCACC-3', R: 5'-ATCTTAGTCTTGAAGTGAGGAT-3')[38] and rs2234922 (F: 5'-TCTGGTGCCAGAGCCTGACCGTGC-3', R: 5'-ATGGAACCTCTAGCAGCCCCGTACC-3')[29] were adapted from published studies and validated using

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NCBI Primer-BLAST[39] to ensure specificity for *EPHX1* and avoid off-target amplification. Primers were synthesised by Genewiz (South Plainfield, NJ, USA), reconstituted, and stored at 4°C prior to further analysis.

PCR amplification was performed for 200 samples per SNP in a final reaction volume of 15 µL, consisting of 5 µL DNA and 10 µL PCR master mix. The PCR master mix included sterile nuclease-free water, primers (forward and reverse), and 5× FIREPol® Master Mix Ready to Load (Solis BioDyne, Tartu, Estonia), which contains 7.5 mM $MgCl_2$ (final concentration 1.5 mM). For rs1051740 (T>C), cycling conditions included initial denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 s, annealing at 54°C for 30 s, and extension at 72°C for 1 min, with a final extension at 72°C for 5 min. For rs2234922 (A>G), initial denaturation was at 95°C for 7 min, followed by 35 cycles of denaturation at 95°C for 1 min, annealing at 64°C for 1 min, and extension at 72°C for 1 min, with a final extension at 72°C for 7 min. Amplified products were stored at 4°C, and a non-template control was included in each run.

PCR products were resolved on 2% agarose gels stained with ethidium bromide and visualised under a UV transilluminator. Band patterns were consistent with expected amplicon sizes, confirming successful amplification. Allele frequencies were determined from genotyping results based on banding patterns observed in agarose gel electrophoresis.

Statistical Analysis: Data from questionnaires and gel electrophoresis were analysed using Microsoft Excel, version 2021. Categorical variables were summarised as frequencies and percentages, and continuous variables as mean ± standard deviation (SD). Binary variables were coded as 'Yes' = 1 and 'No' = 0. Group differences were evaluated using chi-square (χ^2) test, Fisher's exact test (GraphPad QuickCalcs, accessed July 2025), and independent t-tests (Student's or Welch's, as appropriate). Allele frequencies were compared using chi-square (χ^2) test and crude odds ratios (ORs) with 95% confidence intervals (CIs). The crude ORs were further tested for statistical significance using the z-test, p-values were derived from the z-statistics based on the standard normal distribution. Associations with clinical parameters were assessed using Pearson correlation and linear regression, with statistical significance set at $p < 0.05$.

RESULTS

No significant difference was observed in age between the preeclamptic (31.93 ± 4.91 years) and normotensive (30.55 ± 5.73 years) groups ($p = 0.071$) (Table 1). Although height differed significantly ($p = 0.00077$), the difference was not clinically significant. Maternal weight, body mass index (BMI), systolic blood pressure, and diastolic blood pressure were significantly higher in the preeclamptic group ($p < 0.0001$). Proteinuria was strongly associated with preeclampsia ($p < 0.0001$), though isolated cases in normotensive pregnant women likely reflected transient or benign conditions such as dehydration or urinary tract infection.

Table 2 shows the socio-demographic and lifestyle characteristics of preeclamptic and normotensive pregnant women, with data presented as frequencies and percentages.

Hypertension, diabetes mellitus, and a family history of preeclampsia were significantly more prevalent among preeclamptic women compared with their normotensive counterparts ($p < 0.01$), whereas other comorbidities showed no statistical difference between groups ($p > 0.05$). Preeclamptic women exhibited significantly higher frequencies of rapid weight gain, severe headache, dizziness, altered reflexes, and visual disturbances. In contrast, abdominal pain, reduced urine output, and vomiting/nausea did not differ significantly. Nulliparity was observed only among normotensive pregnant women, while primigravida status was slightly less represented in the preeclamptic group (Table 3).

Association of EPHX1 SNPs (rs1051740 and rs2234922) with Preeclampsia: PCR amplification of the target regions encompassing rs1051740 and rs2234922 was confirmed through agarose gel electrophoresis. The resulting allele-specific banding patterns served as indicators of the presence or absence of the respective alleles in both normotensive and preeclamptic samples. Representative gel images are presented in Figure 1.

Figure 2 shows the allele frequencies of rs1051740 and rs2234922 in preeclamptic and normotensive pregnant women. The bar chart depicts the proportional distribution of each allele across the two groups, and the accompanying table summarises the statistical comparisons. For rs1051740, 190 samples were analysed (95 cases and 95 controls) after excluding 10 due to DNA degradation or poor amplification. For rs2234922, all 200 samples were successfully analysed (97 cases and 103 controls).

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For rs1051740 (T>C), the C (His113) allele — the mutant and minor allele was significantly more frequent in preeclamptic women (49.5%) than in normotensive controls (15.8%). In contrast, the T (Tyr113) allele predominated in controls (84.2%) compared with cases (50.5%). Chi-square analysis showed a strong association between allele type and preeclampsia risk ($\chi^2 = 24.52$, df = 1, $p = 7.4 \times 10^{-7}$). The crude odds ratio (OR = 5.22; 95% CI: 2.64–10.34) indicates that the C allele was associated with more than a fivefold increase in the odds of developing PE relative to the wild-type allele. This association was highly significant ($z = 4.7458$; $p = 2.076 \times 10^{-6}$).

For rs2234922 (A>G), the A (His139) allele — the major, wild-type allele was more frequent in preeclamptic women (96.9%) than in normotensive controls (86.4%). Conversely, the G (Arg139) allele was less common in cases (3.1%) compared with controls (13.6%). Chi-square analysis showed a statistically significant association between the A allele and preeclampsia ($\chi^2 = 7.07$, df = 1, $p = 0.00784$). The crude odds ratio (OR = 4.93; 95% CI: 1.37–17.73) indicates that the A allele was associated with nearly a fivefold increased odds of developing PE compared with the G allele. This association was statistically significant ($z = 2.4427$; $p = 0.0146$).

Table 4 summarises associations between rs1051740 and rs2234922 with systolic blood pressure (SBP), diastolic blood pressure (DBP), and maternal weight in preeclamptic and normotensive pregnant women. Allele presence and absence were coded as 1 and 0, respectively. For rs1051740 (T>C), a weak but statistically significant positive correlation with SBP was observed in the preeclamptic group ($r = 0.22$, $p = 0.03$). No significant correlations were observed with DBP or maternal weight in either group, and all other associations were weak ($p > 0.05$). For rs2234922 (A>G), no significant correlations were detected with SBP, DBP, or maternal weight in either group; the strongest trend ($r = 0.17$, $p = 0.11$) was observed with maternal weight in preeclamptic women.

Table 1. Maternal clinical characteristics of preeclamptic and normotensive pregnant women

Clinical Characteristics	Preeclamptic (n = 97) Mean ± SD	Normotensive (n = 103) Mean ± SD	T-test	p value
Maternal Age (Years)	31.93 ± 4.91	30.55 ± 5.73	1.82	0.071
Weight (kg)	85.27 ± 16.91	73.27± 12.61	5.66	5.95×10^{-8}
Height (cm)	157.06 ± 6.68	160.50 ± 7.04	-3.42	0.00077
Body Mass Index -(BMI, kg/m^2)	34.42 ± 6.14	28.32 ± 4.88	7.51	2.65×10^{-12}
Systolic Blood Pressure - (SBP, mmHg)	147.88 ± 11.31	113.97 ± 10.33	22.16	1.57×10^{-55}
Diastolic Blood Pressure - (DBP, mmHg)	88.56 ± 8.61	69.69 ± 8.77	15.35	1.56×10^{-35}
Proteinuria (≥ 1 + on Dipstick)	38 (39.18)	4 (3.88)	—	<0.0001

SD- Standard Deviation

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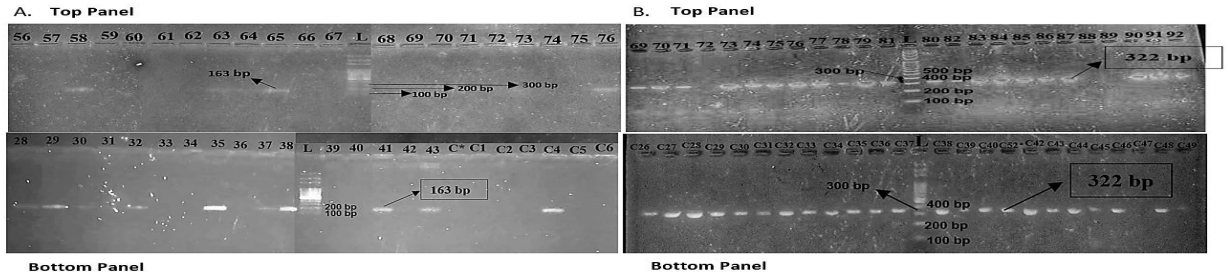
Table 2. Socio-demographic and Lifestyle characteristics of Preeclamptic and Normotensive Pregnant Women

Variable	Preeclamptic (n = 97) - n (%)	Normotensive (n = 103) - n (%)
Socio-demographic Characteristics		
Ethnicity		
Yoruba	58 (59.8)	75 (72.8)
Igbo	17 (17.5)	16 (15.5)
Hausa	1 (1.0)	4 (3.9)
Others	21 (21.6)	8 (7.8)
Occupation		
Employed	19 (19.6)	21 (20.4)
Self-employed	75 (77.3)	71 (68.9)
Non-employed	3 (3.1)	11 (10.7)
Lifestyle Characteristics		
Smoking	2 (2.1)	2 (1.9)
Alcohol Consumption	6 (6.2)	4 (3.9)

Table 3. Comparative analysis of maternal clinical profile in preeclamptic and normotensive pregnant women

Variable	Preeclamptic (n = 97) - n (%)	Normotensive (n = 103) - n (%)	p
Medical History			
Hypertension	70 (72.2)	1 (0.9)	0.0001*
Diabetes Mellitus	8 (8.2)	0 (0)	0.0026*
Chronic Renal Disease	1 (1.0)	0 (0)	0.4850*
Sickle cell Disease	0 (0)	2 (1.9)	0.4979*
Kidney Disease	0 (0)	1 (0.9)	1.0000*
Urinary Tract Infection	8 (8.2)	8 (7.8)	0.9009
Family History of PE	21 (21.6)	0 (0)	0.0001*
Current Clinical Conditions			
Rapid Weight Gain	54 (55.7)	22 (21.4)	< 0.0001
Abdominal Pain	27 (27.8)	29 (28.2)	0.9597
Severe Headache	36 (37.1)	9 (8.74)	<0.0001
Change in Reflexes	23 (23.7)	8 (7.8)	0.0018
Low Urine Output	5 (5.2)	6 (5.8)	0.8353
Dizziness	39 (40.2)	19 (18.4)	0.0007
Excessive Vomiting/Nausea	13 (13.4)	6 (5.8)	0.0678
Vision Changes	17 (17.5)	3 (2.9)	0.0006
Nulliparity	0 (0)	6 (5.8)	0.0293*
Primigravida	31 (31.9)	39 (37.9)	0.3815

Fisher's exact test was applied for variables marked with an asterisk (*)
All other comparisons were performed using the chi-square test



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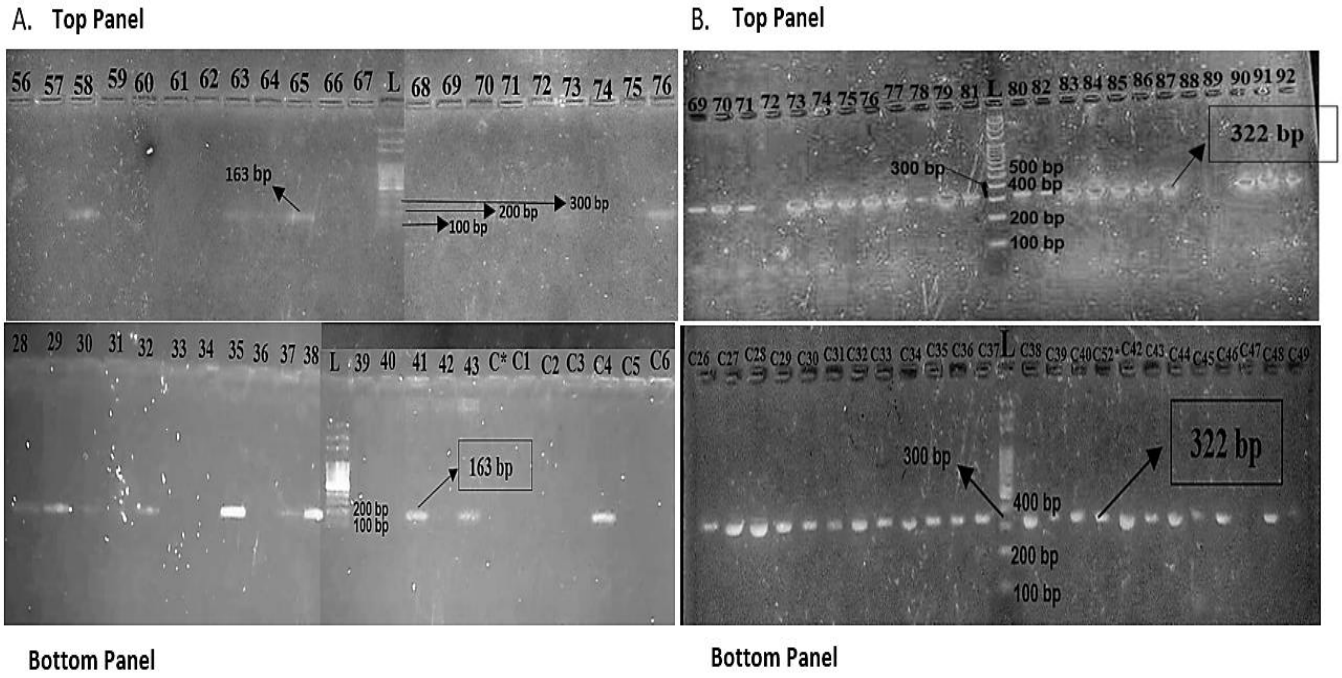

Figure 1. Representative agarose gel electrophoresis images showing allele-specific banding patterns for *EPHX1* SNPs rs1051740 and rs2234922
(A) rs1051740 (T>C; Tyr113His; Exon 3): Normotensive samples are shown in the top panel, and preeclamptic samples in the bottom panel. A 163 bp band corresponds to the mutant C allele (His113), while its absence indicates the wild-type T allele (Tyr113).
(B) rs2234922 (A>G; His139Arg; Exon 4): Normotensive samples are shown in the top panel, and preeclamptic samples in the bottom panel. A 322 bp band corresponds to the wild-type A allele (His139), while its absence indicates the mutant G allele (Arg139).
Arrows indicate the expected allele-specific amplicons and additional bands for size reference. L denotes the DNA ladder used for size comparison.

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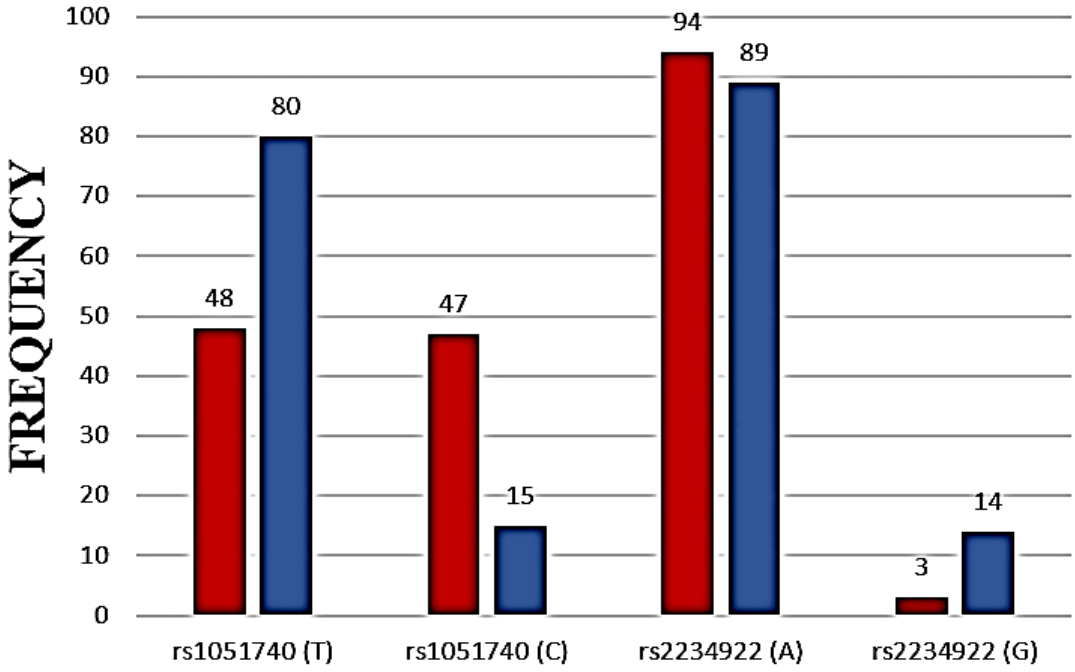

Alleles	Preeclamptic (Cases)	Normotensive (Controls)	Crude OR (95% CI)	p- value
rs1051740	(n = 95) - n (%)	(n = 95) - n (%)		
T (113Tyr)	48 (50.5)	80 (84.2)	5.22 (2.64 — 10.34)	7.4×10^{-7}
C (113His)	47 (49.5)	15 (15.8)		
rs2234922	(n = 97) - n (%)	(n = 103) - n (%)		
A (139His)	94 (96.9)	89 (86.4)	4.93 (1.37 — 17.73)	0.00784
G (139Arg)	3 (3.1)	14 (13.6)		

OR- Odds ratio; CI- Confidence Interval

Figure 2. Comparison of allele frequencies of *EPHX1* SNPs (rs1051740 and rs2234922) in preeclamptic and normotensive pregnant women

Table 4. Correlation of rs1051740 (T>C) and rs2234922 (A>G) polymorphisms with systolic blood pressure, diastolic blood pressure, and maternal weight among preeclamptic (P) and normotensive (N) pregnant women

	Systolic Blood Pressure		Diastolic Blood Pressure		Weight	
	P	N	P	N	P	N
rs1051740 (T>C)						
r-value	0.222	0.103	-0.079	-0.167	-0.086	0.101
p-value	0.030	0.319	0.448	0.107	0.405	0.328
rs2234922 (A>G)						
r-value	0.052	-0.007	0.003	0.018	0.165	0.046
p- value	0.616	0.940	0.979	0.860	0.107	0.645

P – Preeclamptic; N – Normotensive

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DISCUSSION

Oxidative stress and endothelial dysfunction are well established as central mechanisms in the pathogenesis of preeclampsia.[1] Within this context, enzymes involved in xenobiotic metabolism, particularly microsomal epoxide hydrolase 1 (*EPHX1*), contribute to vascular protection by detoxifying reactive epoxides and maintaining endothelial integrity. Functional genetic variation in *EPHX1* has been investigated as a potential modifier of preeclampsia susceptibility.

In this study, we examined the association between two functional *EPHX1* SNPs—rs1051740 and rs2234922—and preeclampsia (PE) risk among Nigerian pregnant women, alongside maternal clinical, lifestyle, and socio-demographic characteristics. To the best of our knowledge, this is the first study to evaluate these SNPs in relation to PE within a Nigerian cohort.

In our study, elevated BMI was significantly associated with PE, consistent with findings by Meazaw et al.[13], whereas Tessema et al.[40] reported normal BMI as protective, underscoring population-specific differences in risk profiles. Notably, nulliparity was observed only among normotensive women, suggesting a protective effect and diverging from Lin et al.[41]

Primigravida status showed no association, aligning with Kassa et al.[42] but differing from Haile et al.[43]. A family history of PE was present exclusively among preeclamptic women, reinforcing evidence of a heritable component.[44] Severe headache was also significantly associated with PE, reflecting its established role in disease severity and vascular dysfunction.[45] Smoking and alcohol consumption were not examined for associations with PE, leaving their potential contribution to gene–environment interactions unaddressed and thereby limiting the scope of the findings.

The major findings of this study revealed significant associations between *EPHX1* SNPs rs1051740 (T>C) and rs2234922 (A>G) with PE. The rs1051740 C allele was strongly associated with increased PE risk, supporting it potential role as a genetic susceptibility marker. This observation is consistent with Lykke et al.[46], who reported a significant association between the CC genotype and severe PE in a Danish cohort. A weak but statistically significant positive correlation was also observed between the C allele and systolic blood pressure in preeclamptic women ($r = 0.222$; $p = 0.030$), indicating a possible association between this variant and blood pressure regulation.

For rs2234922, the A allele (His139) was significantly more prevalent among pregnant women with preeclampsia than in normotensive controls, suggesting a possible link with increased susceptibility to the condition. However, its frequent occurrence among normotensive women indicates that this allele alone is not independently determinative of disease status, underscoring the multifactorial nature of PE. Conversely, the G allele appeared less frequent in preeclamptic women, indicating a possible protective effect. No significant associations were observed between rs2234922 (A>G) and clinical parameters, suggesting that its role may be confined to genetic susceptibility rather than phenotypic expression.

Comparative analysis with previous studies reveals mixed findings. In Finnish women, Laasanen et al.[29] reported no significant single-SNP associations, although their haplotype analysis identified a significant T–A haplotype linked to preeclampsia. By contrast, Groten et al.[47] found a strong association between the Tyr113 allele and severe PE in German and Ghanaian women, while Zusterzeel et al.[28] reported that the TT genotype increased PE risk in Dutch women. In Saudi women, Aljuaid et al.[48] observed no significant associations between these SNPs and PE. Similarly, Kamal et al.[38] found no link between rs1051740 and PE in Egyptian women; however, they reported a significant genotype difference for rs2234922 ($p = 0.002$), with the GG genotype (Arg139–Arg139) occurring exclusively in PE cases. Taken together, these varied findings underscore the importance of considering population-specific genetic backgrounds when investigating PE risk.

Limitations

This study was constrained by certain limitations. Recruitment challenges, particularly in identifying sufficient preeclamptic cases, resulted in a smaller sample size than initially intended. Time constraints further limited participant recruitment.

Although statistically significant associations were observed, their clinical relevance remains uncertain, as *EPHX1* has not been widely featured in large-scale genome-wide studies. Moreover, key non-genetic factors, including socio-demographic characteristics (ethnicity and occupation) and lifestyle behaviors (smoking and alcohol consumption), were not assessed for potential association with preeclampsia. This

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omission may have limited the extent of gene-environment interactions analysis.

Nonetheless, this research provides novel genetic data from Nigerian women and underscores the need for more inclusive investigations.

CONCLUSION

This study presents new evidence linking *EPHX1* polymorphisms to increased preeclampsia risk in Nigerian pregnant women. These findings support the gene's potential involvement in PE pathogenesis, possibly through oxidative stress pathways. Future studies incorporating larger, population-specific cohorts, functional validation, and advanced genotyping methods are essential to clarify *EPHX1's* biological role and its potential utility as a genetic risk marker for preeclampsia. Moreover, integrating analysis of key non-genetic factors will be crucial to capture gene-environmental interactions and provide a more comprehensive understanding of preeclampsia risk.

Declarations

Authors' contribution: TAF – Conceptualisation, Methodology, Supervision, Project Administration, Writing – Review & Editing, Resources. OVJ – Investigation, Formal analysis, Ethical approval acquisition, Visualisation, Writing – Original Draft, Resources. TMO – Investigation, Formal Analysis, Resources. CSO – Investigation, Formal analysis, Resources. PAN – Investigation, Formal analysis, Ethical approval acquisition, Resources. JOA – Investigation, Formal analysis, Ethical approval acquisition, Resources.

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