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Genetic polymorphisms associated with preeclampsia risk in Nigerian women

Mathew F. Olaniyan[1], Obataze J. Akpoyovwere[2], Nwamaka P. Kanikwu[2], Tolulope B. Olaniyan[1], Medinat T. Adeniran[3], Musa A. Muhibi[1] and Odekunle B. Odegbemi[1,4*]

Abstract

Background Preeclampsia, a complex hypertensive disorder unique to pregnancy, significantly impacts maternal and fetal health worldwide, with a prevalence of 2–8%. This condition results from a complex interplay of genetic, environmental, and immunological factors.

Aim and objectives This study aims to investigate the genetic predispositions to preeclampsia, focusing on specific gene polymorphisms among pregnant women at Central Hospital Auchi, Nigeria.

Materials and methods We examined the endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), angiotensin-converting enzyme (ACE), and tumor necrosis factor-alpha (TNF-α) genes in 200 pregnant women, equally divided between preeclamptic patients and normotensive controls.

Results The eNOS G894T polymorphism was significantly associated with preeclampsia, with the T allele nearly doubling the risk. The VEGF C936T polymorphism's T allele also indicated a higher risk. The D allele in the ACE gene's insertion/deletion (I/D) polymorphism significantly increased the risk, as did the A allele in the TNF-α G308A polymorphism.

Conclusions These findings highlight the importance of genetic factors in preeclampsia and suggest that genetic screening could improve risk stratification and early detection. Future research should integrate genetic, epigenetic, and environmental data to understand preeclampsia's multifaceted nature and develop targeted therapies. This study underscores the potential of personalized medicine in managing and reducing the risks associated with preeclampsia.

Keywords Preeclampsia, Genetic polymorphisms, Endothelial nitric oxide synthase (eNOS), Vascular endothelial growth factor (VEGF), Angiotensin-converting enzyme (ACE), Tumor necrosis factor-alpha (TNF-α), Nigeria

Introduction

Preeclampsia, a condition characterized by high blood pressure during pregnancy, remains a significant challenge for maternal and fetal health globally. Its prevalence ranges from 2 to 8% worldwide, contributing significantly to maternal and perinatal morbidity and mortality [1, 2]. The condition's intricate pathophysiology involves genetic, environmental, and immunological factors. Research indicates that genetic susceptibility significantly influences the development of preeclampsia [3]. Advances in genomic technologies have led to identifying several candidate genes associated with an increased risk of this disorder. These findings enhance

*Correspondence:
Odekunle B. Odegbemi
odegbemi21.odekunle@edouniversity.edu.ng
[1] Medical Laboratory Science Department, Edo State University, Uzairue, Edo State, Nigeria
[2] Nursing Science Department, Edo State University, Uzairue, Edo State, Nigeria
[3] Oyo State College of Nursing Oluyoro, Ibadan, Oyo State, Nigeria
[4] Medical Laboratory Science Department, Naval Medical Centre Borikiri, Port Harcourt, Rivers State, Nigeria

our understanding of the molecular mechanisms underlying preeclampsia.

The development of preeclampsia disrupts various physiological processes, including placental development, angiogenesis, and immune regulation [4]. The placenta, essential for nutrient and gas exchange between the mother and fetus, is central to the pathogenesis of preeclampsia. Abnormal placental implantation and inadequate remodeling of spiral arteries can result in placental ischemia and oxidative stress, releasing antiangiogenic factors and inflammatory mediators into the maternal circulation [5, 6].

Environmental factors can significantly increase the risk of preeclampsia. Factors such as air pollution, exposure to heavy metals (e.g., lead and cadmium), poor air quality, and industrial waste have been associated with elevated risk. Women living in areas with high pollution levels or near industries are at greater risk due to chronic inflammation and oxidative stress, which can disrupt normal placental function. Additionally, pesticide exposure and poor water quality have been linked to increased preeclampsia risk, further emphasizing the impact of environmental factors on maternal health [7–11].

Genetic factors contribute to preeclampsia susceptibility through mechanisms involving angiogenesis, immune regulation, oxidative stress, and endothelial dysfunction [12, 13]. Polymorphisms in genes such as vascular endothelial growth factor (VEGF), endoglin (ENG), and soluble fms-like tyrosine kinase-1 (sFLT-1) are linked to an increased risk of preeclampsia [14, 15]. While individual genetic variants have modest effects, the cumulative impact of multiple genetic and environmental factors likely determines the overall risk and severity of preeclampsia [16]. Epigenetic mechanisms, including DNA methylation and histone modifications, also regulate gene expression patterns associated with preeclampsia [17, 18].

Despite significant advances in understanding preeclampsia's genetic and molecular basis, it remains a complex disorder. Continued research integrating genomic, epigenomic, and environmental data is crucial to unravel the factors contributing to its development and progression. Such insights could improve risk stratification, early detection, and targeted therapeutic interventions, reducing the burden of this significant obstetric complication.

Objectives

The specific objectives were to:

1. Identify genes linked to preeclampsia in pregnant women at Central Hospital Auchi.
2. Analyze gene polymorphisms and their role in preeclampsia development.
3. Assess the relationship between these polymorphisms and clinical outcomes in preeclampsia.

Materials and methods

Study population

The study included 200 pregnant women age range of 18–45 years: 100 diagnosed with preeclampsia and 100 normotensive as controls, recruited from Central Hospital Auchi, Edo State (now Edo State University Uzairue Teaching Hospital), Nigeria. Ethical approval was obtained, and informed consent was collected from all participants.

Inclusion criteria

- For preeclamptic patients: Pregnant women aged between 18 and 45 years diagnosed with preeclampsia were recruited.
- For controls: Pregnant women aged between 18 and 45 years who were normotensive, i.e., did not have high blood pressure.

Exclusion criteria

The study excluded women with pre-existing hypertension, multiple pregnancies, or other complications unrelated to preeclampsia.

Sample size calculation

Sample size was calculated using a formula for case–control studies, ensuring statistical power: $n = [Z\alpha/2\sqrt{(2pq)} + Z\beta\sqrt{(p1q1 + p2q2)}]2/(p1 - p2)2$. [19]

where: p1 and p2 are the proportions in the two groups. $q1 = (1 - p1)$ and $q2 = (1 - p2)$. $Z\alpha/2$ is the z-score for the significance level (e.g., 1.96 for $\alpha = 0.05$). $Z\beta$ is the z-score for the power of the study (e.g., 0.84 for 80% power). $(p1 - p2)$ is the expected effect size (the difference between the two groups).

Estimating the parameters

Effect size

The anticipated difference between the case and control groups in a key variable (e.g., proportion of preeclampsia or a biochemical parameter, assume this is 10%).

Proportions

If the expected prevalence in the control group is 10% ($p1 = 0.10 p\_1 = 0.10 p1 = 0.10$) and in the case group is 20% ($p2 = 0.20 p\_2 = 0.20 p2 = 0.20$).

- Significance Level (α): set at 0.05 ($Z = 1.96$).
- Power ($1 - \beta$): Set at 80% ($Z = 0.84$).

Simplified sample size calculation

Using the formula and the following assumed values:

- p1 = 0.10, q1 = 0.90p_1 = 0.10, q_1 = 0.90p1 = 0.10,q1 = 0.90
- p2 = 0.20, q2 = 0.80p_2 = 0.20, q_2 = 0.80p2 = 0.20,q2 = 0.80
  $n = (1.96 \cdot 0.10 \cdot 0.90 + 0.20 \cdot 0.80)2(0.10)2n = \frac{(1.96 \cdot \sqrt{0.10 \cdot 0.90 + 0.20 \cdot 0.80})^2}{(0.10)^2}n = (0.10)2(1.96 \cdot 0.10 \cdot 0.90 + 0.20 \cdot 0.80)2$
- Calculate the first term inside the square root
  $0.10 \cdot 0.90 + 0.20 \cdot 0.80 = 0.09 + 0.16 = 0.25 = 0.5\sqrt{0.10 \cdot 0.90 + 0.20 \cdot 0.80} = \sqrt{0.09 + 0.16} = \sqrt{0.25} = 0.50.10 \cdot 0.90 + 0.20 \cdot 0.80 = 0.09 + 0.16 = 0.25 = 0.5$
- Multiply by $Z\alpha/2$ (1.96)
  $1.96 \cdot 0.5 = 0.981.96 \cdot 0.5 = 0.981.96 \cdot 0.5 = 0.98$
- Square this result
  $0.982 = 0.96040.98^2 = 0.96040.982 = 0.9604$
- Calculate the denominator
  $(0.10)2 = 0.01(0.10)^2 = 0.01(0.10)2 = 0.01$
- Final sample size

$N = 0.9604/0.01 = 96.04$

Thus, approximately 96 subjects per group are required. Rounding this up to 100 subjects per group provides a sample size of 100 cases and 100 controls.

Based on previous studies and anticipated effect size, 100 participants per group were determined sufficient to detect significant differences in gene polymorphisms.

Sample collection and DNA extraction

Venous blood samples (5 mL) were collected from each participant. Genomic DNA was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). DNA concentration and purity were assessed using a NanoDrop spectrophotometer (Thermo Fisher Scientific).

Gene selection and polymorphism analysis

The study focused on genes involved in angiogenesis, immune regulation, and oxidative stress: endothelial nitric oxide synthase (eNOS), VEGF, angiotensin-converting enzyme (ACE), and tumor necrosis factor-alpha (TNF-α). Specific single nucleotide polymorphisms (SNPs) within these genes were analyzed using Polymerase Chain Reaction (PCR) and Restriction Fragment Length Polymorphism (RFLP) techniques. PCR products were digested with restriction enzymes and separated by gel electrophoresis.

Table 1 Genotype frequencies for eNOS (G894T) polymorphism

Genotype	Preeclamptic group (%)	Control group (%)
GG	41.0	56.0
GT	46.0	36.0
TT	13.0	8.0

Table 2 Allele frequencies for eNOS (G894T) polymorphism

Allele	Preeclamptic group (%)	Control group (%)	Odds ratio (95% CI)
T	38.5	24.0	1.98 (1.26–3.11)

Statistical analysis

Genotype and allele frequencies were compared between preeclamptic and normotensive groups. Associations between gene polymorphisms and preeclampsia risk were evaluated using Chi-square or Fisher's exact tests. Logistic regression estimated odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for potential confounding factors. The Hardy–Weinberg equilibrium (HWE) was assessed for each polymorphism. Statistical analyses were performed using SPSS 22.0, with a p value < 0.05 considered statistically significant.

Results

eNOS Gene Polymorphism

The G894T polymorphism in the eNOS gene showed a significant association with preeclampsia. Genotype distribution was GG (41.0%), GT (46.0%), and TT (13.0%) in the preeclamptic group and GG (56.0%), GT (36.0%), and TT (8.0%) in controls. The T allele frequency was higher in the preeclamptic group (38.5% vs. 24.0%, $p = 0.003$). The OR for the T allele was 1.98 (95% CI 1.26–3.11), indicating a nearly two-fold increased risk of preeclampsia (Tables 1 and 2).

VEGF gene polymorphism

The C936T polymorphism in the VEGF gene also showed significant differences between groups. Genotype frequencies were CC (52.0%), CT (40.0%), and TT (8.0%) in the preeclamptic group and CC (73.0%), CT (23.0%), and TT (4.0%) in controls. The T allele frequency was higher in preeclamptic patients (27.5% vs. 14.5%, $p = 0.001$). The T allele conferred an increased risk of preeclampsia, with an OR of 2.24 (95% CI 1.39–3.62) (Tables 3 and 4).

Table 3 Genotype frequencies for VEGF (C936T) polymorphism

Genotype	Preeclamptic group (%)	Control group (%)
CC	52.0	73.0
CT	40.0	23.0
TT	8.0	4.0

Table 4 Allele frequencies for VEGF (C936T) polymorphism

Allele	Preeclamptic group (%)	Control group (%)	Odds ratio (95% CI)
T	27.5	14.5	2.24 (1.39–3.62)

Table 5 Genotype frequencies for ACE (I/D) polymorphism

Genotype	Preeclamptic group (%)	Control group (%)
II	32.0	49.0
ID	48.0	42.0
DD	20.0	9.0

Table 6 Allele frequencies for ACE (I/D) polymorphism

Allele	Preeclamptic group (%)	Control group (%)	Odds ratio (95% CI)
D	44.0	30.0	1.84 (1.17–2.88)

ACE gene polymorphism

The I/D polymorphism in the ACE gene was significantly associated with preeclampsia. Genotype distribution was II (32.0%), ID (48.0%), and DD (20.0%) in the preeclamptic group and II (49.0%), ID (42.0%), and DD (9.0%) in controls. The D allele frequency was higher in the preeclamptic group (44.0% vs. 30.0%, $p=0.008$). The D allele was associated with an increased risk of preeclampsia, with an OR of 1.84 (95% CI 1.17–2.88) (Tables 5 and 6).

TNF-α gene polymorphism

Genotype distribution was GG (64.0%), GA (28.0%), and AA (8.0%) in the preeclamptic group and GG (76.0%), GA (24.0%), and AA (0.0%) in controls. The G308A polymorphism in the TNF-α gene was significantly associated with preeclampsia. The A allele frequency was higher in the preeclamptic group (22.0% vs. 12.0%, $p=0.018$). The A allele was associated with an increased risk of preeclampsia, with an OR of 2.07 (95% CI 1.13–3.79) (Tables 7 and 8).

Table 7 Genotype frequencies for TNF-α (G308A) polymorphism

Genotype	Preeclamptic group (%)	Control group (%)
GG	64.0	76.0
GA	28.0	24.0
AA	8.0	0.0

Table 8 Allele frequencies for TNF-α (G308A) polymorphism

Allele	Preeclamptic group (%)	Control group (%)	Odds ratio (95% CI)
A	22.0	12.0	2.07 (1.13–3.79)

Discussion

This study is the first to investigate the association of specific polymorphisms with preeclampsia (PE) in a South-South Nigerian population, marking a significant contribution to understanding the genetic underpinnings of PE in this region. Our findings confirm that genetic variations in the endothelial nitric oxide synthase (eNOS), vascular endothelial growth factor (VEGF), angiotensin-converting enzyme (ACE), and tumor necrosis factor-alpha (TNF-α) genes significantly increase the risk of PE, supporting their involvement in its pathophysiology.

The eNOS G894T polymorphism emerged as a key determinant, with the T allele nearly doubling the risk of PE in our study population. The association of this polymorphism with impaired nitric oxide production and endothelial dysfunction is consistent with previous studies, which suggest that reduced NO bioavailability contributes to the vascular abnormalities observed in PE [20]. Similarly, the VEGF C936T polymorphism was found to be associated with increased PE risk, particularly due to the T allele. VEGF plays a critical role in angiogenesis and placental vascular development, and disruptions in these processes are central to the pathology of PE [21–24].

The ACE I/D polymorphism also displayed a significant correlation with PE, where the D allele was linked to higher ACE activity and angiotensin II levels, factors known to contribute to hypertension and endothelial dysfunction [25, 26]. Moreover, the TNF-α G308A polymorphism, associated with higher TNF-α levels, indicates the involvement of inflammatory processes in PE development. Elevated TNF-α exacerbates systemic inflammation, a hallmark of PE, further confirming its role in the disease mechanism [27].

Our study also highlights the importance of gene–gene interactions. The combined effects of these polymorphisms likely exert a stronger influence on PE risk than individual variants alone. For instance, the interaction between the eNOS and VEGF gene polymorphisms could exacerbate endothelial dysfunction and impaired angiogenesis, while the ACE and TNF-α interactions may amplify inflammatory responses. Future research should focus on exploring these gene–gene and gene-environment interactions to better understand the multifactorial nature of PE [28, 29].

This investigation emphasizes the necessity for genetic screening in at-risk populations, particularly in regions like South-South Nigeria, where environmental and genetic factors may differ from other populations. The integration of genetic data with clinical and environmental information could lead to personalized approaches for PE management, targeting women with specific genetic predispositions [30].

Our findings underscore the complex genetic landscape of PE and the critical role of gene interactions in shaping disease risk. Further studies incorporating larger sample sizes and diverse populations will be instrumental in confirming these associations and elucidating the mechanisms by which these polymorphisms contribute to PE.

Conclusion

This research examined the relationship between genetic polymorphisms in several candidate genes and the likelihood of developing preeclampsia in pregnant women at Central Hospital Auchi, Edo State, Nigeria. The study identified significant correlations between specific gene polymorphisms—specifically, eNOS G894T, VEGF C936T, ACE I/D, and TNF-α G308A—and the incidence of preeclampsia. These findings highlight the critical role of genetic factors in developing preeclampsia and suggest the potential benefits of genetic screening and risk assessment in managing this complex condition. By enhancing our understanding of the molecular mechanisms involved in preeclampsia, this study supports the need for further research that combines genomic, environmental, and clinical data to create targeted therapeutic and preventive measures.

Limitations of the study

1. Although the sample size was statistically sufficient, larger cohorts are needed to validate the results and enhance their applicability.
2. The study did not consider gene–gene and gene-environment interactions, which could affect preeclampsia risk assessment.
3. Conducted within a specific population, the findings may not be generalizable to diverse genetic backgrounds.
4. The lack of functional analyses limited our understanding of how the identified polymorphisms contribute to the pathogenesis of preeclampsia.

Recommendations

1. Conduct more extensive cohort studies to validate findings across diverse populations.
2. Use genome-wide association studies (GWAS) to identify additional genetic factors.
3. Examine the combined effects of gene–gene and gene-environment interactions on preeclampsia risk.
4. Investigate the molecular mechanisms through functional studies to identify potential therapies.
5. Develop personalized medicine approaches tailored to individual genetic profiles for better management and prevention.

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Author contributions
MFO conceptualized the research, participated in research design and overall research supervision. OJA participated in research design and sample collection. NPK participated in research design and sample collection. MAA participated in the research design and data analysis. TBO participated in sample collection, sample analysis and manuscript writing. MTA participated in research design and data collation. MAA coordinated sample collection and analysis. OBO participated in research design, data analysis, and manuscript writing.

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Availability of data and materials
All data and study materials are available on request.

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Edo State University School of Postgraduate Studies Research Ethics Committee, and informed consent was collected from all participants.

Consent for publication
All authors consent to this publication.

Competing interests
The authors declare that there are no competing interests.

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