ASSOCIATION OF mtDNA COPY NUMBER, GLUCOCORTICOID RECEPTOR, AND INFLAMMATORY GENES POLYMORPHISMS WITH PROSTATE CANCER AMONG WEST AFRICAN MEN

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A DISSERTATION SUBMITTED TO THE SCHOOL OF POSTGRADUATE STUDIES IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF MASTER OF SCIENCE, (M.Sc.) IN BIOCHEMISTRY IN THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF SCIENCE AND TECHNOLOGY, COVENANT UNIVERSITY, OTA, NIGERIA

FEBRUARY, 2024

ACCEPTANCE

This is to attest that this dissertation is accepted in partial fulfillment of the requirements for the award of a Master of Science (M.Sc.) in Biochemistry in the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Nigeria.

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Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

DECLARATION

I, **OLASEHINDE, OLUTOLA ESTHER**, hereby declare that I carried out this research work under the supervision of Prof. Solomon O. Rotimi (Supervisor) of the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State. I attest that the dissertation has not been presented either wholly or partially for the award of any degree elsewhere. All sources of data and scholarly information used in this dissertation were duly acknowledged.

OLASEHINDE, OLUTOLA ESTHER

Signature and Date

CERTIFICATION

We hereby, certify that this dissertation titled " **ASSOCIATION OF mtDNA COPY NUMBER, GLUCOCORTICOID RECEPTOR, AND INFLAMMATORY GENES POLYMORPHISMS WITH PROSTATE CANCER AMONG WEST AFRICAN MEN**" is an original research work carried out by **OLASEHINDE, OLUTOLA ESTHER** with matriculation number **(16CP021227)** from the Department of Biochemistry, College of Science and Technology, Covenant University, Ota, Ogun State, Nigeria, under the supervision of Prof SOLOMON O. ROTIMI. We reviewed the work and determined that it meets the requirements for the award of the degree of Master of Science (M.Sc.) in Biochemistry.

Prof. Solomon O. Rotimi
(Supervisor) **Signature and Date**

Prof. Solomon O. Rotimi
(Head of Department) **Signature and Date**

Prof. Oluwatosin B. Adu
(External Examiner) **Signature and Date**

Prof. Akan B. Williams
(Dean, School of Postgraduate Studies) **Signature and Date**

DEDICATION

This dissertation is dedicated to God for his never-ending faithfulness and help throughout the course of this project. This dissertation is also dedicated to my role model and loving mother Professor Grace I. Olasehinde who helped me to navigate my academic career and stood by me till the very end.

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LIST OF ABBREVIATIONS

ASIR – Age-Standardized Incidence Rate

CI - Confidence Interval

GR – Glucocorticoid Receptor

HDI - Human Development Index

IFN-L4 – Interferon Lambda 4

IL6 – Interleukin 6

IL8 - Interleukin 8

LL- Lower Limit

mtDNA – Mitochondrial DNA

mtDNA-CN – Mitochondrial DNA Copy Number

PCa – Prostate Cancer

SNPs – Single Nucleotide Polymorphisms

UL - Upper Limit

ABSTRACT

Prostate cancer (PCa) is the second most common malignancy diagnosed in men and the fifth leading cause of cancer death worldwide. It is characterized by considerable geo-ethnic disparity, with men of African descent showing an approximately 2.7-fold higher mortality rate than the global average. Altered levels of mitochondrial DNA copy number (mtDNA-CN) have been associated with a higher risk of PCa and changes in prostate glandular architecture, suggesting it is a potential cancer marker. Single nucleotide polymorphisms (SNPs) within the glucocorticoid receptor (GR) and inflammatory genes have been shown to induce modifications in signaling pathways and immunomodulatory responses. These genetic alterations have been implicated in amplifying the aggressiveness of PCa. This study aimed to determine the relationship between the mtDNA-CN, GR polymorphisms, and inflammatory genes polymorphisms among PCa patients recruited from Nigeria, Niger, and Benin Republic. The case-control study consisted of 166 PCa patients and 200 paired healthy controls. Multiplex qPCR was used to measure mtDNA-CN levels and TaqMan genotyping assay was used to determine the genotypes of GR - Tth111I (rs10052957), ER22 (rs6189), 23 EK (rs6190), NR3C1-1 (rs10482605), BclI (rs41423237), and 9β (rs6198) and inflammatory genes-IL-8(rs4073), IL-6(rs1800795), IFN-L4(rs-368234815) polymorphisms. The study found that PCa patients exhibited significantly elevated ($p= 1.867e^{-06}$) mtDNA-CN compared to healthy controls. Pairwise comparisons between the GR SNPs showed a high linkage disequilibrium (LD) for 9β and Tth111I ($D' = 1$, $r^2 = 0.083$), BCL1 and Tth111I ($D'= 0.782$, $r^2 = 0.42$) in controls. High LD was also observed for BCL1 and Tth111I ($D'= 0.773$, $r^2 = 0.511$) and Intermediate LD for 9β and Tth111I ($D' = 1$, $r^2 = 0.04$) in cases. In conclusion, this study offers suggestive evidence regarding the impact of mtDNA-CN levels and SNPs on the susceptibility to PCa among West African men.

Keywords: mtDNA-CN, GR, PCa, SNPs, IL6, IL8, IFN-L4