Role of SLC6A4 Gene in Serotonin Levels, Gonadocorticoids and Inflammation on the Severity of Depression in Patients from Nigeria

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Being a PhD Thesis Submitted to the Department of Biological Science, Faculty of Natural and Applied Sciences, Lead City University, Ibadan, Oyo State, Nigeria

In Partial Fulfilment for the degree of the Requirements For the Award of Doctor of Philosophy (PhD) in Molecular Biology and Genomics

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2025

Certification

This is to certify that Obianuju Ibifuro OJIKAH with matriculation number: LCU/PG/000253 carried out this research work titled "**Role of SLC6A4 Gene in Serotonin Levels, Gonadocorticoids and Inflammation on the Severity of Depression in Patients from Nigeria"** in the Department of Biological Sciences, Faculty of Natural and Sciences, Lead City University, Ibadan Oyo State, Nigeria, for the award of **Doctor of Philosophy Degree (PhD) in Molecular Biology and Genomics** and has not been partly or completely submitted for a degree in this university or any other university.

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Supervisor

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Dr. O. C. Bakare Date
Head of Department

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Dedication

I want to dedicate this work to God Almighty, my Mother, Barr. Mrs. Helen Jack-Ojikah and my Grand Mother, Madam Caroline Walson-Jack, who are my inspiration on my most trying days. I am forever grateful.

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Even though the aforementioned individuals and persons assisted in this research work, I am solely accountable for all oversights, if any, that may have been made in my work.

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Abstract

Depression is a complex disorder influenced by genetic, environmental, and hormonal factors. Sex, age-related differences alongside lifestyle choices play a a dynamic role in the concurrence of depression and its severity in men and women. The SLC6A4 gene, responsible for serotonin transporter regulation, has been implicated in depression. However, the relationship between SLC6A4 gene variants, serotonin levels, gonadocorticoids, inflammation, and depression severity in Nigerian patients remains unexplored. This study investigated the association between gene- environmental factors, serum serotonin, IL-6 and gonadocorticoids levels on depression severity in Nigerian patients. Ethical clearance was obtained from the Federal Ministry of Health with approval number: NHREC/01/01/2007-01/09/2024. A case-control study was conducted, 164 participants, 73 with depression and 91 healthy controls were recruited. 10 mls of blood samples were collected from all participants, After consent was given, two questionnaires were issued and enrolment characteristics were recorded. qPCR genotyping of SLC6A4 gene variants, rs6354 and rs8076005, serum serotonin and IL-6 were estimated by ELISA kits. Progesterone, testosterone and estrogen were quantified with CLIA microparicles kits. The results show that SLC6A4 long or short alleles were not present in this population. rs6354 played a role in severe depression (p=0.035). Significantly levels of reduced serum serotonin levels (p= <0.001) and testosterone (p=0.024) in the cases, compared to controls. Males testosterone levels was significantly increased in severe depression (p= 0.033). Both rs8076005 and rs634 the recessive homozygous alleles were risk factors for low serotonin levels (p= <0.001). Il-6 levels showed protective traits in women who were diagnosed with depression (p= 0.048). Employment and alcohol consumption were also found to protect against odds of depression occurrence. Lifestyle choices such as smoking, and number of children or lack of, did not show any noticeable associations to depression, neither did progesterone or oestrogen. This study provides evidence for the role of lifestyle, SLC6A4 gene in modulating serotonin levels, as well as hormonal factors, which contribute to the severity of depression in men and women in Nigeria. This study highlights the complex interplay between biological factors in depression and underscores the need for personalized treatment approaches. The findings of this study contribute to our understanding of the biological mechanisms underlying depression and have implications for the development of novel therapeutic strategies.

Keywords: Depression, Polymophism, Serotonin, Inflammation, Gonadocorticiods,

Nigeria.

Word Count: 368 words.

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Table of Contents

Content	Page
Certification	ii
Dedication	iii
Acknowledgement	iv
Abstract	vi
Table of Contents	i
List of Tables	vi
List of Figures	viii
List of Plates	ix
List of Appendixes	x
List of Acronyms	xi
Chapter One	**Error! Bookmark not defined.**
Introduction	**Error! Bookmark not defined.**
1.1 Background to the Study	**Error! Bookmark not defined.**
1.2 Statement of the Problem	**Error! Bookmark not defined.**
1.3 Justification of the Study	**Error! Bookmark not defined.**
1.4 Aim and Objectives of the study	**Error! Bookmark not defined.**
1.5 Research Questions	**Error! Bookmark not defined.**
1.6 Hypotheses	**Error! Bookmark not defined.**
1.7 Significance of the Study	**Error! Bookmark not defined.**
1.8 Scope of the Study	**Error! Bookmark not defined.**
1.9 Limitations	**Error! Bookmark not defined.**
1.10 Operational Definition of Terms	**Error! Bookmark not defined.**
Endnotes	**Error! Bookmark not defined.**

Lead City University Ibadan DO NOT COPY

Chapter Two **Error! Bookmark not defined.**

Literature Review **Error! Bookmark not defined.**

2.1 History of Depression **Error! Bookmark not defined.**

2.1.1 Earliest Account **Error! Bookmark not defined.**

2.1.2 Ancient Greek and Roman Philosophy **Error! Bookmark not defined.**

2.1.3 Common Era **Error! Bookmark not defined.**

2.1.4 Age of Enlightenment **Error! Bookmark not defined.**

2.1.5 19th and 20th Century **Error! Bookmark not defined.**

2.1.6 Modern Times **Error! Bookmark not defined.**

2.2 Major Depressive Disorder (MDD) **Error! Bookmark not defined.**

2.2.1 Other Types of Depression **Error! Bookmark not defined.**

2.2.2 Signs and Symptoms **Error! Bookmark not defined.**

2.2.2.1 Depression in Children And Adolescents **Error! Bookmark not defined.**

2.2.2.2 Depression in Senior Citizens **Error! Bookmark not defined.**

2.2.3 Causative Agents **Error! Bookmark not defined.**

2.2.4 Risk Factors **Error! Bookmark not defined.**

2.2.5 Diagnosis **Error! Bookmark not defined.**

2.2.6 Prevention **Error! Bookmark not defined.**

2.2.7 Treatment **Error! Bookmark not defined.**

2.2.7.1 Typical Side Effects **Error! Bookmark not defined.**

2.2.7.2 Potential Hazards to Health **Error! Bookmark not defined.**

2.2.8 Prognosis **Error! Bookmark not defined.**

2.2.9 Statistics **Error! Bookmark not defined.**

2.2.9.1 Statistics of Depression Around the World **Error! Bookmark not defined.**

2.2.9.2 Statistics of Depression in Nigeria **Error! Bookmark not defined.**

Lead City University Ibadan DO NOT COPY

2.3 The Brain- The Vagus Nerve- The Gut **Error! Bookmark not defined.**

2.4 Serotonin: The Neurotransmitter **Error! Bookmark not defined.**

2.4.1 Possible Genetic Linkages of Depression **Error! Bookmark not defined.**

2.4.2 Inflammation- Associated Genes **Error! Bookmark not defined.**

2.4.3 Neuroplasticity **Error! Bookmark not defined.**

2.4.4 Neurotransmitters **Error! Bookmark not defined.**

2.4.5 Stress-Associated Genes **Error! Bookmark not defined.**

2.4.6 Whole-Genome Transcriptome Assays **Error! Bookmark not defined.**

2.5 The SLC6A4 Gene (Solute Carrier Family 6 Member 4) **Error! Bookmark not defined.**

2.5.1 Gene Location **Error! Bookmark not defined.**

2.5.2 Gene Size/Genomic Content **Error! Bookmark not defined.**

2.5.3 General Information **Error! Bookmark not defined.**

2.5.4 Transcription of Human SLC6A4 Gene **Error! Bookmark not defined.**

2.5.5 Human SCL6A4 Protein **Error! Bookmark not defined.**

2.5.6 Human SCL6A4 Expression **Error! Bookmark not defined.**

2.6.7 Human SCL6A4 Localisation **Error! Bookmark not defined.**

2.5.8 Other Biological Functions of SLC6A4 Gene **Error! Bookmark not defined.**

2.5.9 Mutations of the SLC6A4 Gene **Error! Bookmark not defined.**

2.6 5HTTLPR and the SNPs **Error! Bookmark not defined.**

2.6.1 SLC6A4 Phenotypes, Serotonin Levels and Depression **Error! Bookmark not defined.**

2.6.2 Sex Difference In Depression **Error! Bookmark not defined.**

Endnotes **Error! Bookmark not defined.**

Lead City University Ibadan DO NOT COPY

Chapter Three **Error! Bookmark not defined.**

Methodology **Error! Bookmark not defined.**

3.1 Study Design and Sample Size **Error! Bookmark not defined.**

3.2 Ethical Approval, Consent, Confidentiality and Withdrawal **Error! Bookmark not defined.**

3.3 Inclusion/Exclusion Criteria **Error! Bookmark not defined.**

3.4 Sample Type, Collection and Processing **Error! Bookmark not defined.**

3.5 Data Collection, Management and Statistical Analysis **Error! Bookmark not defined.**

3.6 Anticipated Issues and Expected Outcomes **Error! Bookmark not defined.**

3.7 Project Plan and Implementation **Error! Bookmark not defined.**

3.7.1 Dissemination of Study Findings **Error! Bookmark not defined.**

3.8 Monitoring and Evaluation Plan **Error! Bookmark not defined.**

3.9 Responsibility/Litigation **Error! Bookmark not defined.**

3.10 Laboratory Procedures and Analysis **Error! Bookmark not defined.**

3.11 Copy Number Variation and Single Nucleotide Polymorphism (SNP) Sequencing and Selection **Error! Bookmark not defined.**

3.12 Managing and Storing Samples **Error! Bookmark not defined.**

3.13 Whole Blood Extraction **Error! Bookmark not defined.**

3.14 DNA Quality and Concentration **Error! Bookmark not defined.**

3.15 qPCR Procedure for SLC6A4 (CNV) **Error! Bookmark not defined.**

3.16 Serum/Plasma Serotonin and Interleukin (IL-6) levels using Enzyme-Linked Immunosorbent Assay (ELISA kits) **Error! Bookmark not defined.**

Lead City University Ibadan DO NOT COPY

3.17 Serum Testosterone, Estrogen and Progesterone using Chemiluminescent Microparticle Immunoassay (CLIA Microparticles) **Error! Bookmark not defined.**

Endnotes **Error! Bookmark not defined.**

Chapter Four **Error! Bookmark not defined.**

Results and Discussion of Findings **Error! Bookmark not defined.**

4.1 Results of Findings **Error! Bookmark not defined.**

4.2 Discussion of Findings **Error! Bookmark not defined.**

Endnotes **Error! Bookmark not defined.**

Chapter Five **Error! Bookmark not defined.**

Conclusion **Error! Bookmark not defined.**

5.1 Summary of Findings **Error! Bookmark not defined.**

5.2 Conclusion **Error! Bookmark not defined.**

5.3 Recommendations **Error! Bookmark not defined.**

5.4 Contribution to Knowledge **Error! Bookmark not defined.**

5.5 Suggested Areas for Future Research **Error! Bookmark not defined.**

Bibliography **Error! Bookmark not defined.**

Appendices **Error! Bookmark not defined.**

Bio-data **Error! Bookmark not defined.**

The University Compliance Certification **Error! Bookmark not defined.**

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List of Tables

Tables	Title	Page
2.1	Transcripts of Human SLC6A4 Gene	69
2.2	Mutations of the SLC6A4 Gene	77
2.3	SNPs and Their Associated Conditions	83
3.1	Kits Contents for Whole Blood Extraction	120
3.2	The Extraction Procedure of Libex Nucleic Acid Extraction	121
3.3	PCR Reactions for Copy Number Experiments	126
3.4	PCR Reactions for Genotyping Experiments	127
3.5	Genotyping Experiments: Fast Cycling	129
3.6	Materials Provided with ELISA Kit	132
3.7	ELISA Dilution Standard	134
3.8	Reagent Pack for CLIA Micro particles	138
4.1	Study Populations' Enrollment Data	147
4.2	Study Populations' SLC6A4 Genomic Data	153
4.3	SNP Phenotype Distribution between the Case and Control	155
4.4	SNP Phenotype Distribution between the HDRS Groups	157
4.5	rs8076005 Hardy Weinberg Phenotype and Allele Distribution between the Depression Strata and Control	159
4.6	rs6354 Hardy Weinberg Phenotype and Allele Distribution between the Depression Strata and Control	161
4.7	Distribution of Severity of Depression by Cohort and Sex	163

Lead City University Ibadan DO NOT COPY

4.8 Age Distribution of Participants Stratified by Depression and Control 165

4.9 Association of Age Distribution and Presence of Children on Case and Control 167

4.10 Association of Socio-economic Factors in Case and Control Groups 169

4.11 Association of Socio-economic Factors in HDRS Groups 171

4.12 Comparison of Age and Serological Variables of Participants across Control and Case Groups 174

4.13 Comparison of Variables of Participants Based on Severity of Depression for the Overall Population and Stratified by Sex 179

4.14 Distribution of Serotonin Levels Among the SNPs 183

4.15 Associations between the SNP's Genotypic and Allelic Distribution and Serotonin Levels 185

4.16 Descriptive and Two-Factor ANOVA Statistics of Variables Based on Severity of Depressive for Male Subjects 187

4.17 Descriptive and Two-Factor ANOVA Statistics of Variables Based on Severity of Depressive for Female Subjects 189

4.18 Inter-Correlation Coefficients Between Variables for Males and Females 191

4.19 Diagnostic Test Accuracy Measures of Sex and Inflammatory Hormones Levels for Predicting Depression and Varying Severity of Depressive Symptoms In Males 193

4.20 Diagnostic Test Accuracy Measures of Sex and Inflammatory Hormones Levels for Predicting Depression and Varying Severity of Depressive Symptoms In Females 195

Lead City University Ibadan DO NOT COPY

List of Figures

Figure	Title	Page
2.2	Pathophisiology of Depression	28
2.3	Statistics of Major Depression in American Population	39
2.4	The Brain-Gut Micrbiota in Depression	43
2.5	Central Nervous System (CNS) and Gut Cycle in Depression	45
2.6	Cytogenic Location of SLC6A4	65
2.7	Numbers and Illustrative Sizes of Exons of Humans SLC6A4 gene	66
2.8	Genomic Location SLC6A4	67
2.9	Structure of Human Solute Carrier Family 6 member 4	71
2.10	Expression Profile of SLC6A4 in Different Tissues/Organs in Humans	73
2.11	Serotogenic Synapse Pathway Map	75
2.12	Serotogenic Neurotransmitter and SLC6A4	81
4.1	Average Age Among the Study Population	149
4.2	Hamilton Depression Rating Scale (HDRS) Among Test & Control Group	151
4 3	Serological Concentrations Between Depression & Control in Men and Women	175
4.4	Serological Concentration Between Depression & Control in Men and Women	176
4.5	Hormonal Distribution in Male and Female Population Based on Severity of Depression	180
4.6	Hormonal Distribution in Male and Female Population Based on Severity of Depression	181

Lead City University Ibadan DO NOT COPY

4.7 Receiver Operating Characteristics (ROC) curves of Sex and Inflammatory Hormones in Males 196

4.8 Receiver Operating Characteristics (ROC) curves of Sex and Inflammatory Hormones in Males 197

4.9 Linear Regression Analyses of Serotonin versus Interleukin-6 (a) Males and (b) Females 198

List of Plates

Plate Title **Page**

2.1 Pictorial diagram of a statue Greek physician Hippocrates 15

Lead City University Ibadan DO NOT COPY

List of Appendixes

Appendix	Page
1: Ethical Clerance Letters	228
2: Hamilton Depressive Rating Scale	235
3: Socio-Economic Quesstionnnaire	237
4: Consent Form	240
5: Confidentialty Agreement	245
6: Gene Assay Information	250
7: Turnitin Score	253
8. Collaboators	258

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List of Acronyms

Abbreviation	Meaning
17q11.1-17g12	Genomoic Location of the Slc6a4 Gene.
5-HIAA	5-hydroxyindoleacetic acid
5HTT	5-hydroxytryptamine
5HTTLPR	5-hydroxytryptamine Transporter Linked Polymorphism Region
AA	Amino Acid
ADHD	Attention Deficit/hyperactivity Disorder
AEOs	Acid Extractable Organic Compounds
AIM2	Absent in MelanomaProtein
ANOVA	Analysis of Variance
AOEs	Antioxidant Enzymes
ASC	Apoptosis-Associated Speck-Like Protein
ASD	Autism Spectrum Disorder
BBB	Blood-Brain Barrier
BCE	Before the Common Era
BDNF	Brain-Derived Neurotrophic Factor
BP	Base Pair
BPD	Bipolar Disorder
CAT	Catalse

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CBT	Cognitive Behavioural Therapy
C-C motif	Chemokine motif
CE	Common Era
CLIA	Chemiluminescent Microparticle Immunoassay
CNS	Central Nervous System
CNV	Copy Number Variation.
DSM III	Diagnostic and Statistical Manual of Mental Disorders 3rd edition
DSM IV	Diagnostic and Statistical Manual of Mental Disorders 5th edition
DSM	Diagnostic and Statistical Manual of Mental Disorders.
ECT	Electroshock Therapy
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme Linked- Imunoassay
EPK	Eukaryotic Protein Kinase
EPO	Erythropoietin
FCT	Federal Capital Territory
GABA	Gamma-aminobutyric acid
GENDEP	Genome-Based Therapeutic Drugs for Depression
GI	Gastrointestinal Tract
GL	Glutathione Reductase
GLUT1,3	Glucose Transporter-1,3
GPM6A	GlycoProtein M6a
GRE	Glucocorticoid Responsive Elements
HDRS	Hamilton Depressive Rating Scale

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HIF-1	Inducible Factor-1
HIV/AIDS	Human Immune Virus/ Acquired Immunodeficiency Disorder.
HPA	Hypothalamic-Pitutary-Adrenal
HTT	Hydroxytryptamine Transporter
ICD	International Classification of Diseases and Health Related Problems
IDPs	Internally Displaced Persons
IL-1	Interluekin-1
IL-1b	Interluekin-1b
IL-6	Interluekin-6
L/L	Long/Long Phenotype of the SLC6A4 gene
L/S	Long/Short Phenotype of the SLC6A4 gene
LDHA	Lactate Dehydrogenase-A
MAO	Monoamine oxidase
MAOA	Monoamine oxidase A
MAOIs	Monoaminine Oxidase Inhibitors
CD	Compulsive Disorder
MDD	Major Depressive Disorder
MEK	Mitogen-activated Protein Kinase
MIF	Macrophage Inhibiting Factor
MnSOD	Manganese Superoxide Dismutase
mRNA	messenger Ribonucleic Acid
Na/K	Sodium-Potassium Pump
NDA	Non-Disclosure Agreement

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NSAID	Non-Sterioidal Antiiflammatory drugs
NTS	Nucleus Tractus Solitarius
OCD	Obsessive Compulsive Disorder.
OXT	Oxytocin
OXTR	Oxytocin Receptor
PAMP	Pathogen-Associated Molecular Pattern
PGK1	Phosphoglycerate Kinase 1
pH	Potential of Hydrogen
PLP	Proteolipid Protein
qPCR	Quantitative Polymerase Chain Reaction
ROS	Reactive Oxygen Species
rs	Reference Cluster
S/S	short/short phenotype of the SLC6A4 gene
SCFAs	Short-Chain Fatty Acids
SCL6A4	Solute Carrier Family 6 member 4
SERT	Serotonin Transporter
SNMs	Serotonin Norephine Reuptake Inhibitors.
SNP	Single Nucleotide Polymophism
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TCF4	Transcription Factor 4
TLR-3	Toll-like receptor 3
TLR-4	Toll-like receptor 4
TMS	Transcranial Magnetic Stimulation
TNF	Tumor Necrosis Factor

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TW	Treatment Weeks
VNS	Vagus Nerve Stimulation
VNTR	Variant Number Tandem Repeat
WHO	World Health Organisation

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