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

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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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Head of Department

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.

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.

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