Study of the Role of Brain-Derived Neurotrophic Factor (BDNF) Val66Met Genetic Polymorphism and Serum BDNF in the Phenotypic Expression of Mood disorders in a Sample of Egyptian Patients

Thesis

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Abstract

Background: There is substantial evidence that Brain Derived Neurotrophic Factor is involved in the aetiology of mood disorders, however genetic studies assessing the relationship between BDNF and these disorders have produced conflicting results

Aim of the study: to investigate the association of BDNF Val66Met polymorphism and serum BDNF with mood disorders per se as well with specific phenotypic aspects in these disorders in a sample of Egyptian patients

Methods: A case control study including 62 patients with the diagnoses of bipolar and major depression disorders and 31 controls. The two groups of patients were assessed clinically and were subjected to Hamilton Depression Rating scale, Young Mania Rating scale and Child Traumatic Questionnaire, in addition to the neurocognitive and personality assessment which were administrated to all participants. Serum BDNF levels were determined by using ELISA and Genotyping of Val66Met polymorphism by Real Time Polymerase Chain Reaction(PCR) **Results:** The serum BDNF level in the control group was found higher than both groups of patients, and this difference was statistically significant between the bipolar group and the control group as well as between the bipolar and the major depression groups of patients .No statistical significant difference between the 3 groups regarding the three genotypes of the Val 66 Polymorphism, but there was a statistical significant difference concerning the relation between the risky genotypes in both groups of patients and certain clinical aspects and some of the Wisconsin indices of the WCST.

Conclusion: Lower serum BDNF level may be considered a state dependent biomarker of mood episodes in patients with Bipolar disorder. This study suggests that the Val66Met polymorphism is not associated with both bipolar and unipolar disorders but related to certain clinical features and executive dysfunction in these disorders in a sample of Egyptian patients. Childhood abuse is a risk factor for more severe clinical characteristics in patients with bipolar and major depression disorders

Keywords: BDNF-Serum - Polymorphism - Bipolar -Major depression -WCST- Childhood abuse

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List of Abbreviations

ABCC1	:	ATP-Binding cassette, subfamily c, member 1
ACC	:	Anterior cingulate cortex
ACTH	:	Adrenocorticotropic hormone
AD	:	Alzheimer's disease
ADHD	:	Attention deficit hyperactivity disorder
ADRB1	:	Beta-1-adrenergic receptor
AM	:	Autobiographical memory
AMPA	:	α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANK3	:	Ankyrin-3
APOE	:	Apolipo-protein E
ATP	:	Adenosine triphosphate
AVP	:	Arginine vasopressin
BA	:	Brodmann area
BAD	:	Bcl-2-associated death promoter
Bcl-2	:	B-cell lymphoma 2
bcl-2	:	B-cell lymphoma protein-2
BCST	:	Berg Card Sorting Test
BDNF	:	Brain-derived neurotrophic factor
BMAL1	:	Brain and Muscle ARNT-like Protein-1
BPD	:	Bipolar disorder
CA1	:	Region I of hippocampus proper *(cornus ammonis)*
CACNA1C	:	Calcium channel, voltage-dependent, L type, alpha 1C subunit
CBF	:	Cerebral blood flow
CGT	:	Cambridge Gamble Test
Clock	:	Circadian Locomotor Output Cycles Kaput.
cM	:	Centimorgans
COMT	:	Catechol-o-methyltransferase
COS-7	:	CV-1 in Origin with SV40 genes(African Green Monkey *Cercopithecus aethiops* Fibroblast-like Kidney Cells
CREB1	:	cAMP responsive element binding protein 1
CRH	:	Corticotrophin-releasing hormone
CRHR1	:	Corticotropin-releasing hormone receptor 1
CRP	:	C-reactive protein
CSDS	:	Chronic social defeat stress
CSF	:	Cerebrospinal fluid
CTQ	:	Child Traumatic Questionnaire
DA	:	Dopamine
DGKH	:	Di-acyl-glycerol kinase eta
DISC1	:	Disrupted in schizophrenia 1
DLPC	:	Dorsolateral prefrontal cortex
DNA	:	Deoxyribonucleic acid
DNMTs	:	DNA methyltransferases

DRD2	:	Dopamine receptor D2
DSM- IV-TR	:	Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition- text revision
DTNBP1	:	Dystrobrevinbinding- protein 1
DZ	:	Dizygotic
eCB	:	Endocannabinoid system
ECT	:	Electroconvulsive therapy
ELS	:	Early life stress
EPQ	:	Eysenck's Personality Questionnaire
ERK-MAP	:	Extracellular-signal-regulated kinases- mitogen activated protein
FKBP5	:	Glucocorticoid receptor-regulating cochaperone
FKBP5	:	FK506 binding protein 5
GABA	:	γ-aminobutyric acid
GENDEP	:	Genome-based Therapeutic Drugs for Depression
GenRED	:	Genetics of Recurrent Early-Onset Depression
GFAP	:	Glial fibrillary acidic protein
GHQ – 12	:	General health Questionnaire-12
GluR1	:	Glutamate receptor 1
GR	:	Glucocorticoid receptor
GRIK4	:	Glutamate receptor, ionotropic, kainate 4
GRM7	:	Glutamate receptor metabotropic 7
GSK	:	Glycogen synthase kinase
GSK-3	:	Glycogen synthase kinase 3
GWAS	:	Genome wide association studies
H3K27	:	Histone 3 lysine 27
HATs	:	Histone acetyltransferases
HDAC5	:	Histone deacetylase 5
HDACs	:	Histone deacetylases
HDRS	:	Hamilton Depression Rating scale
HPA	:	Hypothalamic–pituitary–adrenal axis
HPA	:	Hypothalamic-pituitary-adrenocortical
HSPA5	:	Heat shock protein A5
HVA	:	Homovanillic acid
IGT	:	Iowa Gambling Task
IL	:	Interleukin
IL1B	:	Interleukin 1-beta
IMP	:	Inositol monophosphatase
JAM3	:	Junctional adhesion molecule 3
Kb	:	Kilobase
LCSPT	:	Limbic-cortical-striatal-pallidal-thalamic circuits
LOD	:	Logarithm of the odds
MAOA	:	Monoamine oxidase isoenzyme A
MARS	:	Munich Antidepressant Response Signature
MDD	:	Major depression disorder

MEK	:	Mitogen extracellular signal-regulated kinase
Met	:	Methionine
MHPG	:	3-methoxy-4-hydroxyphenylglycol
MMP	:	Matrix metalloproteinase
MPFC	:	Medial prefrontal cortex
MRI	:	Magnetic resonance imaging
mRNA	:	Messenger ribonucleic acid
MRS	:	Magnetic resonance spectroscopy
mTOR	:	Mammalian target of rapamycin
MZ	:	Monozygotic
NAA	:	N-acetyl-aspartate
NE	:	Norepinephrine
NGF	:	Nerve growth factor
NMDA	:	N-methyl-D-aspartate receptor
NMDA	:	N-methyl-D-aspartate
NOS	:	Nitric oxide synthase
NR3C1	:	Nuclear receptor subfamily 3, group C, member 1
NT-3	:	Neurotrophin-3
NTFs	:	Neurotrophic factors
NTR	:	Neurotrophin receptor
NTRK2	:	Neurotrophic tyrosine kinase receptor, type 2
PAG	:	Periaqueductal gray
PCR	:	Polymerase Chain Reaction
PDE	:	Pyridoxinedependent epilepsy
PDLIM5	:	PDZ and LIM domain 5
PDs	:	Personality disorders
PER 1	:	Period circadian protein homolog 1
PFC	:	Prefrontal cortex
PI-3K	:	Phosphatidylinositol 3-kinase
PKA	:	Protein kinase A
PKC	:	Protein kinase C
POE	:	Parent-of-origin effect
PPIEL	:	Peptidylprolyl isomerase E-like
proBDNF	:	Pro-brain-derived neurotrophic factor
PTSD	:	Post-traumatic stress disorder
PVN	:	Paraventricular nucleus
Raf	:	Rapidly Accelerated Fibrosarcoma
Ras	:	GTP-binding switch protein (*rat sarcoma)*
REM	:	Rapid eye movement
RORA	:	Related orphan receptor A
ROS	:	Reactive oxygen species
rs	:	Reference single nucleotide polymorphism
SCID	:	Structured Clinical Interview for DSM-IV Axis I Disorders
SCN	:	Suprachiasmatic nucleus

sgACC	:	Subgenual anterior cingulate cortex
SLC39A3	:	Solute Carrier Family 39 (Zinc Transporter), Member 3
SNP	:	Single nucleotide polymorphism
SSAT1	:	Spermidine/spermine N (1)-acetyltransferase
SSRIs	:	Selective serotonin reuptake inhibitors
STAR*D	:	Sequenced Treatment Alternatives to Relieve Depression
STEP	:	Systematic Treatment Enhancement Program
SZ	:	Schizophrenia
T4	:	Thyroxine
TCAs	:	Tricyclic antidepressants
TNF	:	Tumor necrosis factor
ToM	:	Theory of Mind
TPH2	:	Neuronal tryptophan hydroxylase
Trk	:	Tropomyosin-related kinase
TrkB	:	Tropomyosin receptor kinase B
UCLA	:	University of California, Los Angeles
UST	:	Uronyl-2-solfotransferase gene
UTR	:	Untranslated region
uVNTR	:	Upstream variable number tandem repeat region.
Val	:	Valine
VPA	:	Valproate
VTA	:	Ventral tegmental area
WAIS-R	:	Wechsler Adult Intelligence Scale- Revised
WCST	:	Wisconsin Card Sorting Test
WGS	:	Wide genome scan studies
WMH	:	White matter hyper-intensities
WTCCC	:	Wellcome Trust Case Control Consortium
YMRS	:	Young Mania Rating Scale
5-HIAA	:	5-hydroxyindoleacetic acid
5HT1B	:	Serotonin receptor 1B
5HT3A	:	Serotonin receptor 3A
5HTT LPR	:	Serotonin-transporter-linked polymorphic region

List of Figures

List of Tables

Contents

INTRODUCTION

Mood disorders, mostly represented by major depressive disorder (MDD) and bipolar disorder (BPD), are the most prevalent psychiatric conditions. They are also among the most severe and debilitating ***(Hashimoto, 2010).***

Major depressive disorder (MDD) is a serious disorder that affects approximately 17% of the population at some point in life, resulting in major social and economic consequences. There is still very little known about the neurobiological alterations that underlie the pathophysiology or treatment of MDD. Several lines of evidence suggest that depression in most people is caused by interactions between a genetic predisposition and some environmental factors ***(Belmaker and Agam, 2008).***

Bipolar disorder (BD) is a highly disabling chronic mood disorder characterized by the presence of manic and depressive symptoms and a lifetime prevalence of 3.9% ***(Yatham et al., 2009)***. Epidemiological studies indicate a role for both biological and environmental factors in the ethiopathogenesis of BD. Due to the high heritability and familial relative risk reported in BD, there is little doubt that molecular genetics play an important role. However, the genetic basis for this illness remains elusive ***(Barnett and Smoller, 2009).***

The precise neurobiology underlying mood disorders is currently unknown. One way to combat these disorders would be to discover novel biomarkers for them, which potentially could revolutionize their recognition and management ***(Lakhan et al., 2010).***

Identification of biomarkers would aid both in the diagnosis, and in the development of effective psychiatric medications to treat them. In addition, biomarkers could provide the basis for early intervention and prevention efforts targeting at-risk individuals.

There are recent findings on the role of brain-derived neurotrophic factor (BDNF) in the pathophysiology of mood disorders ***(Hashimoto, 2010).*** BDNF is a member of the neurotrophin superfamily responsible for promoting and modifying growth, development, and survival of neuronal populations ***(Duman and Monteggia et al., 2006).***

The BDNF gene, which is located on chromosome11 has become a candidate gene for molecular-genetic studies of mood disorders and schizophrenia, and also for pharmacogenomics of drugs used in the treatment of these conditions, such as mood-stabilizers in bipolar mood disorder, antidepressants in depression, and antipsychotics in schizophrenia. It has been demonstrated that the functional Val66Met polymorphism of the gene can be associated with a number of clinical and pharmacological phenomena in these