Genetics and Obsessive Compulsive Disorder Symptoms

Thesis

Submitted for Partial Fulfillment of the Master Degree in Neuropsychiatry

By Lamyaa Abdel Azim El-Toukhy

MBBCH, FACULTY OF MEDICINE AIN SHAMS UNIVERSITY

Under Supervision of **Prof. Nahla El-Sayed Nagy**

Professor of Psychiatry
Faculty of Medicine – Ain Shams University

Dr. Doha Mostafa El Serafi

Assistant Professor of Psychiatry
Faculty of Medicine – Ain Shams University

Dr. Nashwa El Khazragy

Consultant of Clinical Pathology Faculty of Medicine – Ain Shams University

> Faculty of Medicine Ain Shams University CAIRO, 2016



First of all thanks to **ALLAH** the most merciful, for granting me the power to proceed and accomplish this work

Secondly, it has been a long journey leading up to the completion of this thesis. This dissertation would not have been possible without the help, support and patience of my principal supervisor of this thesis: **Prof. Nahla El Sayed Nagy**, Professor of Psychiatry at Faculty of Medicine - Ain Shams University, I would like to sincerely thank her for her outstanding support, supervision and expert guidance.

I would also like to sincerely thank **Dr. Doha Mostafa El Serafi**, Assistant professor of Psychiatry, Faculty of Medicine - Ain Shams University, for her help, constructive criticism, elegant viewpoints and keen insights.

It is my pleasure also to thank **Dr. Nashwa El Khazragy**, Consultant of Clinical Pathology, Faculty of Medicine - Ain Shams University for her time and for her great effort she has done for us.

Also, special thanks to **Dr. Mohamed Youssef**, Assistant lecture my mentor for all his care, support and endless help.

I really appreciate and would like to thank all the patients of our enrolled study for their cooperation and their trust to us. I am also grateful to my family especially my beloved parents. Furthermore, I am grateful to my friends, they continually supported me without any hesitation. Without their support, none of this would ever be possible. I am also grateful to my, sister and brother, for their understanding, patience, and help. Finally, thanks for the nurse staff whom supported me and cooperated without any hesitation.



My thesis is dedicated to my patients, parents, professors, my sister, brother, nephew and my friends; I wish to make them all proud of me.

Lamyaa Eltoukhy

Contents

Title	$Page\ No.$
Introduction	1
Rationale of the study	4
Hypothesis of the study	5
Aim of work	6
Review of Literature:	
• Chapter (1): Overview	w of Obsessive Compulsive
Disorder	7
• Chapter (2): Genetic	s in Obsessive-Compulsive
Disorder	33
• Chapter (3): Implicat	ions of the Genetic Basis on
Future Perspective	59
Subjects and Methods	83
Results	99
Discussion	115
Limitations	
Summary	128
Conclusion	
Recommendations	
References	
Arabic Summary	

List of Tables

Table N	o. Title	Page No.
Table (1):	Candidate genes	43
Table (2):	Phenotypic features frequently described onset OCD patients	•
Table (3):	Comparison of prevalence rates of OCI disorders in family studies	
Table (4):	Molecular findings associated to speciphenotypes	
Table (5):	Presents the results from some studies of the clinical features characterizing the OCD phenotype	tic-related
Table (6):	Neuropsychiatric disorders found more in relatives of OCD probands	
Table (7):	Phenotypic features described as pred worst treatment response (pharmacolog cognitive behavioral) in OCD	gical and
Table (8):	The association of mean age in years a different studied groups	· ·

Table (9):	The association of gender among the different studied groups
Table (10):	Distribution of different OCD Phenotypes among OCD group
Table (11):	Association of different DLCP1 genotypes among the studied groups
Table (12):	Association of different DLGAP1 genotypes and gender of studied groups
Table (13):	Correlation between DLCP1 genotype versus different OCD phenotypes
Table (14):	DLCP1 C/T gene expression allelic frequencies among OCD group
Table (15):	Distribution of C, T alleles frequencies among different studied groups
Table (16):	Correlations between C/T alleles frequencies and different OCD phenotypes
Table (17):	Correlations between C/T alleles frequencies and severity of OCD symptoms

List of Figures

Figure No	o. Title	Page No.
Figure (1):	Poor prognosis of OCD	29
Figure (2):	OCD and related disorders	72
Figure (3):	Schematic diagram of the 5' nuclease	e assay 91
Figure (4):	Amplification plots for DLCP1 polymorphism for different genotype TT, CT), C allele is labeled by V allele is labeled by FAM	es (CC, VIC, T
Figure (5):	Association of DLGAP1 polymorphism genotype among group (OCD/ Control)	studied
Figure (6):	The association of DLCP1 polymorphism genotypes among d OCD phenotypes	ifferent
Figure (7):	Association of allelic frequency studied group (OCD / Control)	

Abbreviations

48-bpVNTR.	Variable number of tandem repeat polymorphisms
5-HT	5-hydroxytryptamine receptors (Serotonin receptors)
5HT1-D	Serotonin 1-D receptor
5HT2A	Serotonin 2- A receptor
5HT2B	Serotonin 2-B receptor
5HT2C	Serotonin 2-C receptor
5HTB	Serotonin B receptor
5ΗΤDβ	Serotonin Dβ receptor
5-HTT	Serotonin transporter gene
5-HTTLPR	Serotonin transporter linked polymorphic region
A	Adenine
ABI	Application binary interface
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactive disorder
AE buffer	Elution buffer
ANOVA	Analysis of variance
AVP	Arginine vasopressin
AW	Washing buffer
BDD	Body dysmorphic disorder
BDNF	Brain derived neurotrophic Growth Factor
C	Cytosine
C°	Degrees Celsius

C9orf68......Chromosome 9 open reading frame 68
CatCatalogue
ChChromosome
CNS.....Central nervous system

COMTCatechol-O-methyltransferase

CYPCytochrome P450

DA..... Dopamine

DAT Dopamine transporter

DLGAP..... Disks large associated proteins

DM......Dorsomedial

DNA.....Deoxyribonucleic acid

DRD......Dopamine receptors

DSM..... Diagnostic and Statistical manual of Mental Disorders

DZ.....Dizygotic

EAACExcitatory amino acid carrier

EAAT.... Excitatory amino acid transporters

ECA Epidemiology catchment Area

EDTA..... Ethylene-diamineteraacetic acid (edetic acid)

EEG..... Electroencephalogram

ESR.... Estrogen receptor α gene

FAIM.....Fas Apoptotic Inhibitory Molecule

FAM....6-carboxyfluorescein.

GABBR.....GABA type B receptor

GAD.....Generalized anxiety disorder

GRIK......Kainate class glutamate receptors GRIN2B......Glutamate Receptor Ionotropic N-Methyl D-Aspartate 2B **GWAS.....** Genome wide association study HIV......Human immunodeficiency virus **HTR1B**5-Hydroxytryptamine (Serotonin) Receptor 1B HTR1B5-Hydroxytryptamine (Serotonin) Receptor 1B HTR2A5-Hydroxytryptamine (Serotonin) Receptor 2A HTR2C5-Hydroxytryptamine (Serotonin) Receptor 2C **ICD**International Classification of Diseases **ID**.....Identification IFD.....Idiopathic focal dystonia **IOCDF-GC....** International OCD Foundation Genetics Collaborative MAO-A..... Monoamine oxidase- A Met......Methionine MGBMinor groove binder Ml.....Milliliter MOG......Myelin oligodendrocyte glycoprotein MZMonozygotic N.....Number NAc......Nucleus accumbens NFQNon fluorescent quencher NmNanometer NMDA N-methyl-D-aspartate No......Number