



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY



Molecular prediction of response to second-generation anti-psychotic drugs in patients with schizophrenia

Thesis

Submitted for partial fulfillment of master degree in neuropsychiatry

By

Mona Hasan Mohamed

M.B.B.Ch, Cairo University

Under supervision of

Prof. Dr. Nahla Elsayed Nagy

Professor of psychiatry

Faculty of Medicine- Ain Shams University

Prof. Dr. Doha Mostafa Elserafy

Professor of psychiatry

Faculty of Medicine- Ain Shams University

Dr. Nashwa Elsayed Nagy

Consultant of clinical pathology

Faculty of medicine, Ain shams university

**Faculty of Medicine
Ain -shams University
2021**

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لسبحناك يا معلم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgment

First of all, thanks to Allah whose magnificent help was the mainfactor in completing this work.

I would like to express my deepest gratitude and thanks to Prof. Dr. Nahla Elsayed Nagy, Professor of psychiatry, Faculty of Medicine, Ain Shams University, For giving me the honor of being her candidate, working underher supervision, guided by her experience and precious advice, and true concern.

Words could not express my great appreciation, thanks and respect to Prof. Dr. Nahla Elsayed Nagy, Professor of psychiatry, Faculty of Medicine, Ain Shams University, for his kindness, patience, consideration, precious assistance throughout this work.

Words could not express my great appreciation, thanks and respect to Dr. Nashwa Elsayed Nagy, Consultant of clinical pathology, Faculty of Medicine, Ain Shams University, for his kindness, patience, consideration, precious assistance throughout this work.

Last, but not least, I would like to express my appreciation and thanks to my family and endless love, the light and the only support of my life my mother



Mona Hasan Mohamed

LIST OF CONTENTS

Title	Page No.
LIST OF CONTENTS	I
List of Tables.....	II
List of Figures	III
Abstract.....	VII
Introduction	1
Aim of the Work.....	6
Review of Literature	7
Antipsychotics	7
Genes and psychotic disorders.....	33
Genes and Treatment	38
Genes and drugs	45
Subjects and methods	56
Results	61
Discussion.....	88
Summary.....	100
Conclusion and Recommendation	103
References	105

List of Tables

Table No.	Title	Page
Table (1):	Comparison between Group A: Olanzapine and Group B: Risperidone according to their baseline characteristics regarding age (years), Gender, Age of onset (years), Duration of disease (months), Family history and Dose (mg).....	61
Table (2):	Comparison between Group A: Olanzapine and Group B: Risperidone according to their response.....	65
Table (3):	Comparison between Group A: Olanzapine and Group B: Risperidone according to their gene expression (FC).....	66
Table (4):	Comparison between Group A: Olanzapine and Group B: Risperidone according to their PANSS.....	68
Table (5):	Association between response “resistant and improved” according to their parameters characteristics regarding Age (years), Gender, Age of onset (years), Duration of disease (months), Family history and Dose (mg) in Group A: Olanzapine.....	70
Table (6):	Association between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” and SLC22A “FC” in Group A: Olanzapine.....	72
Table (7):	Association between response “resistant and improved” according to their parameters characteristics regarding Age (years), Gender, Age of onset (years), Duration of disease (months), Family history and Dose (mg) in Group B: Risperidone.....	74
Table (8):	Association between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” and SLC22A “FC” in Group B: Risperidone.....	77
Table (9):	Correlation between Gene expression (HMOX1 “FC” & SLC22A “FC”) in each group.	79
Table (10):	Correlation between Gene expression (HMOX1 “FC” & SLC22A “FC”) with Age (years), Age of onset (years), Duration of disease (months), Dose (mg) and Reduction of PANSS in Group A: Olanzapine.....	80
Table (11):	Correlation between Gene expression (HMOX1 “FC” & SLC22A “FC”) with Age (years), Age of onset (years), Duration of disease (months), Dose (mg) and Reduction of PANSS in Group B: Risperidone.	82
Table (12):	Association between response “resistant and improved” according to their parameters characteristics regarding Age (years), Gender, Age of onset (years), Duration of disease (months), Family history and Dose (mg) in all patients.	85
Table (13):	Association between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” and SLC22A “FC” in all patients.	86

List of Figures

Fig No.	Title	Page
Fig (1):	Examples of SLC mediated drug transport across the blood-brain barrier and in glioblastomas and neurons.	52
Fig. (2):	Bar chart between Group A: Olanzapine and Group B: Risperidone according to their age (years).	63
Fig. (3):	Bar chart between Group A: Olanzapine and Group B: Risperidone according to their gender.	64
Fig. (4):	Bar chart between Group A: Olanzapine and Group B: Risperidone according to their dose “mg”.	64
Fig. (5):	Bar chart between Group A: Olanzapine and Group B: Risperidone according to their response.	65
Fig. (6):	Box plot between Group A: Olanzapine and Group B: Risperidone according to their HMOX1 (FC).	67
Fig. (7):	Box plot between Group A: Olanzapine and Group B: Risperidone according to their SL C22A (FC).	67
Fig. (8):	Bar chart between Group A: Olanzapine and Group B: Risperidone according to their reduction of PANS.	69
Fig. (9):	Bar chart association between response “resistant and improved” according to their duration of disease “months” in Group A: Olanzapine.	71
Fig. (10):	Box plot between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” in Group A: Olanzapine.	73
Fig. (11):	Box plot between response “resistant and improved” according to their Gene expression regarding SLC22A “FC” in Group A: Olanzapine.	73
Fig. (12):	Bar chart association between response “resistant and improved” according to their duration of disease “months” in Group B: Risperidone.	75
Fig. (13):	Bar chart association between response “resistant and improved” according to their family history in Group B: Risperidone.	76
Fig. (14):	Bar chart association between response “resistant and improved” according to their dose “mg” in Group B: Risperidone.	76
Fig. (15):	Box plot between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” in Group B: Risperidone.	78
Fig. (16):	Box plot between response “resistant and improved” according to their Gene expression regarding SLC22A “FC” in Group B: Risperidone.	78
Fig. (17):	Scatter plot; significant negative correlation between HMOX1 “FC” and SL C22A “FC”	79

Fig. (18): Scatter plot; significant positive correlation between HMOX1 “FC” and reduction of PANSS.	80
Fig. (19): Scatter plot; significant negative correlation between SL C22A “FC” and reduction of PANSS.	81
Fig. (20): Scatter plot; significant negative correlation between SL C22A “FC” and duration of disease.	81
Fig. (21): Scatter plot; significant positive correlation between HMOX1 “FC” and duration of disease.	83
Fig. (22): Scatter plot; significant positive correlation between HMOX1 “FC” and Dose “mg”.	83
Fig. (23): Scatter plot; significant positive correlation between HMOX1 “FC” and reduction of PANSS.	84
Fig. (24): Box plot between response “resistant and improved” according to their Gene expression regarding HMOX1 “FC” in all patients.	87
Fig. (25): Box plot between response “resistant and improved” according to their Gene expression regarding SLC22A “FC” in all patients.	87

List of Abbreviations

Abb.	Full term
5HT	5 hydroxy tryptamine
AD	Alzheimer's disease
ADRs	adverse drug reactions
AP	antipsychotic
BBB	blood brain barrier
BCSFB	blood cerebrospinal fluid barrier
CATIE	clinical antipsychotic trials of intervention effectiveness
cDNA	circular deoxy nucleic acid
CNS	central nervous system
CSF	cerebrospinal fluid
CUTLESS	cost utility of latest antipsychotic drugs in schizophrenia study
DRA	dopamine receptor antagonists
ECT	electroconvulsive therapy
EMA	european medicine agency
EPS	extrapyramidal side effects
FDA	food and drug administration
FGADs	first generation antipsychotics
GAF	global assessment if functioning
GTH	glutathion hydrogenase
GWAS	genome wide adsociation study
HMOX-1	heme oxygenase-1
OLA	olanzapine

PANSS	positive and negative symptoms scale
PBP	psychotic bipolar
PCR	polymerase chain reaction
PD	parkinson's disease
PMs	poor metabolizers
RCT	randomized controlled trial
SAD	schizoaffective disorder
SCID	structured clinical interview for DSM-IV
SCZ	schizophrenia
SGA	second generation antipsychotics
SLC	solute carrier
SLC22A	solute carrier 22A
SSRIs	selective serotonin reuptake inhibitor
TRS	treatment resistant schizophrenia
UMs	ultrapid metabolizers

Abstract

Background: Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, makes it a disabling disorder for many patients and their families.

Aim of the Work: The purpose of our study is to evaluate the potential role of SLC22A and HMOX-1 genes in the prediction of response to second-generation antipsychotic agents

Patients and Methods: This study is prospective cohort study , was conducted on sixty patients with schizophrenia underwent testing with PCR for both SLC22A and HMOX-1 genes. They were divided into 2 groups; group (A) received olanzapine and group (B) received risperidone and followed up for 6 weeks then response was assessed .

Results: there was highly statistically significant positive correlation between treatment resistance and high gene expression of HMOX-1 gene, and statistically significant negative correlation between treatment resistance and high expression of SLC22A gene

Conclusion:HMOX-1 and SLC22A are good predictors for response to second-generation antipsychotic agents.

Key words: schizophrenia , prediction of response, olanzapine, risperidone.

Introduction

Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, make it a disabling disorder for many patients and their families (*Lavretsky 2008*).

Disability often results from both negative symptoms (characterized by loss or deficits) and cognitive symptoms, such as impairments in attention, working memory, or executive function. (*Crismon et al 2014*). In addition, relapse may occur because of positive symptoms, such as suspiciousness, delusions, and hallucinations. The inherent heterogeneity of schizophrenia has resulted in a lack of consensus regarding the disorder's diagnostic criteria, etiology, and pathophysiology. (*Krishna et al 2014*)

Schizophrenia has a substantial genetic component, with a high heritability (up to 80%), indicating that about 80% of the variation in the trait of schizophrenia may be attributed to genetic factors. Genome wide association studies (GWASs), which compare the genomes of thousands of healthy and affected individuals, have found several genes associated with increased risk of developing schizophrenia, such as *NRGN* and *ZNF804A* (*Williams et al 2011*). Recent research suggest that genetic risk for schizophrenia is composed of many common genetic alterations, each with a small effect, along with a few

uncommon genetic alterations with a larger impact. Additionally, genes that confer risk for schizophrenia may also be associated with bipolar disorder and other psychiatric disorders (*Roberts et al 2016*).

Antipsychotic medications are the mainstay of schizophrenia treatment. They are also used for several other clinical conditions i.e., other psychoses, bipolar disorder, delirium, depression, personality disorders, dementia and autism; and are therefore one of the most widely used and costly types of drugs having experienced a significant increase in overall prescription in recent years (*Kantor et al 2015*).

Unfortunately, only 55%–60% of first episode patients will have significantly reduced the severity of their psychopathology with adequate doses of antipsychotic drugs and 30% of patients will fail to respond to two antipsychotics after adequate trials (*Pouget et al 2014*). Research to find predictors of the response to antipsychotic treatment is an old field of psychiatry; however, despite decades of research to find clinical biomarkers, there is not a useful molecular test available to predict the response to treatment (*Prata et al 2014*).

Various environmental factors may interact with susceptibility genes to increase the risk of schizophrenia; these interactions are the focus of an emerging area of investigation called epigenetics. One of the few replicated findings in this relatively new field is an interaction between cannabis use and the AKT1 gene on the risk of psychosis (*Aleman et al 2013*).