شبكة المعلومات الجامعية

التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم

HANAA ALY

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جامعة عين شمس

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قسم

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

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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

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بسم الله الرحمن الرحيم

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Mona Hasan Mohamed

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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	ultrarapid 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 ***(Alemany et al 2013).***