CLINCAL SIGNIFICANCE OF CYP2D6*4 POLYMORPHYSM IN PATIENTS WITH LIVER CIRRHOSIS

Thesis

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By

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Lamiaa Reda El Nashar

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List of Abbreviations

AAT	**:**	Alpha-1 antitrypsin
Ah receptor	**:**	Aryl hydrocarbon receptor
AIH	**:**	Autoimmune hepatitis
ALL	**:**	Acute lymphoblastic leukemia
ANLL	**:**	Acute nonlymphoblastic leukemia
AST/ALT	**:**	Aspartte aminotrasnferase/Alanine aminotransferase ratio
AST/ALT ratio, AAR	**:**	The ratio of aspartate aminotransferase to alanine aminotransferase
ATP-Binding Cassette	**:**	**A**TP-**B**inding **C**assette
AUC	**:**	Area under the curve
BCS	**:**	Budd-chiari syndrome BCS
BMI	**:**	Body mass index
CF	**:**	Cystic fibrosis
CFLD	**:**	Cystic fibrosis liver disease
CFTR	**:**	Cystic fibrosis transmembrane conductance regulator
CHC	**:**	Chronic hepatitis
CML	**:**	Chronic myelogenous leukemia
CT	**:**	Computed tomography
CYP	**:**	Cytochrome P450
CYP2D6	**:**	Cytochrome P450 2D6

ddNTPs	**:**	Dideoxynucleotides
DM	**:**	Diabeties mellitus
dNTPs	**:**	Deoxynucleotides
ECM	**:**	Extracellular matrix
EDHS	**:**	Egyptian Demographic Health Survey
EIA	**:**	Enzyme immunoassay
ELF	**:**	Enhanced liver fibrosis
ELISA	**:**	Enzyme linked immunosorbent assay
EMs	**:**	Extensive metabolizers
ER	**:**	Endoplasmic reticulum
FAD	**:**	Flavin adenine dinucleotide
FHF	**:**	Fulminant Hepatic Failure
FMN	**:**	Flavin mononucleotide
Galactose-1-P	**:**	Galactose-1-phosphate
GALT	**:**	Galactose-1-phosphate uridyl-transferase
GSH	**:**	Glutathione
HA	**:**	Hyaluronic acid
HBV	**:**	Hepatitis B virus
HCC	**:**	Hepatocellular carcinoma
HCV	**:**	Hepatitis C virus
HDV	**:**	Hepatitis D virus
HH	**:**	Hereditary hemochromatosis
HSC	**:**	Hemapoietic stem cell
IFN-α	**:**	Interferon alpha
IFN-β	**:**	Interferon beta

IFN-γ	**:**	Interferon gamma
IHC	**:**	Immunohistochemistry
IMs	**:**	Intermediate metabolizers
IR	**:**	Insulin resistance
MDR	**:**	Multidrug resistance
MMPs	**:**	Metalloproteinases
MRI	**:**	Magnetic resonance imaging
NADH	**:**	Nicotinamide adenine dinucleotide phosphate
NADPH	**:**	Nicotinamide adenine dinucleotide phosphate
NAFLD	**:**	Nonalcoholic fatty liver disease
NAPQI	**:**	Metabolite-acetyl-p-benzoquinoneimine
NASH	**:**	Non-alcoholic steato-hepatitis
NIBMs	**:**	Noninvasive biochemical markers
NT-proCNP	**:**	Anti-human amino-terminal propeptide of C-type natriuretic peptide
PAH	**:**	Polycyclic aromatic hydrocarbons
PBC	**:**	Primary biliary cirrhosis
PDGF	**:**	Platelet derived growth factor
PICP	**:**	Procollagen type I carboxy terminal Peptide
PICP	**:**	Procollagen 1 C peptide
PIIINP	**:**	Procollagen III ammino peptide
PMs]	**:**	Poor metabolizers

PPARgamma	**:**	Peroxisome proliferator-activated receptor gamma
PSC	**:**	Primary sclerosing cholangitis
RIA	**:**	Radioimmunoassay
SDS	**:**	Sodium dodecyl sulfate
SREBP1	**:**	Sterol regulatory element binding protein 1
TGF-β_1	**:**	Transformmg growth factor β_1
TGF-β1	**:**	Transforming growth factor beta 1
TNF-α	**:**	Tumor necrosis factor alpha
UDP galactose	**:**	Uridine diphosphate galactose
UMs	**:**	Ultrarapid metabolizers
WD	**:**	Wilson's disease
WHO	**:**	World Health Organization
γ-GT	**:**	Gamma Glutamyl Transferase

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Introduction

Cirrhosis is the pathological replacement of functional liver tissue with scarred, fibrous and nonfunctional tissue ***(Böhm et al., 2010)***. Most forms of late-stage chronic liver disease often manifest cirrhosis**.** Worldwide, cirrhosis prevalence is increasing with rising incidence of its primary risk factors which include hepatitis virus infection, alcoholism, and non-alcoholic fatty liver disease, however it has many other possible causes ***(Schuppan et al., 2014).***

Cirrhosis is the 10^{th} leading cause of death for men and the 12^{th} for women worldwide. It was found that 7% of all Egyptian deaths annually are associated with either liver cirrhosis or hepatocellular carcinoma, 75-85% of persons with these conditions have either chronic hepatitis B virus infection or hepatitis C virus infection as a contributing cause **(*Poynard et al., 2012).***

Liver biopsy is currently considered the gold standard for assessing cirrhosis. However, it is an invasive and painful procedure, with rare but potential life threatening complications, limiting its acceptance and repetition in asymptomatic patients. In addition, the accuracy of liver biopsy in assessing cirrhosis may be questioned because of

sampling error and interobserver variability, which may lead to underestimating of cirrhosis ***(Muriel and Arauz, 2010).*** Liver biopsy has high specificity (81%-99%) but low sensitivity (36%-57%). Thus there is a need to develop and validate non-invasive tests that can accurately reflect the full spectrum of cirrhosis, and its severity in liver diseases ***(FitzGerald et al., 2012).***

Cytochrome P450 is an enzyme that is encoded by the CYP2D6*4 gene. CYP2D6*4 gene is primarily expressed in the liver. It is also highly expressed in the central nervous system. The cytochrome P450 enzyme system consists of a superfamily of hemoproteins that catalyze the oxidative metabolism of a wide variety of exogenous chemicals including drugs and carcinogens ***(Kotlyar et al., 2005).*** Cytochromes P450 enzymes are the most important enzymes in phase I metabolism in liver ***(Llerena et al., 2009).***

Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. CYP2D6 is perhaps the most extensively studied polymorphically expressed drug metabolizing enzyme in humans and its polymorphism has a high clinical importance ***(Wang et al., 2009).***

The mechanism of hepatotoxicity of drugs is often unknown, but in some instances the pathogenesis of toxic reactions has been shown to be due to CYP-dependent formation of a reactive metabolite of the parent compound. Drug metabolism is impaired in patients with liver cirrhosis, particularly that mediated by CYP2D6*4, but the usefulness of measuring CYP2D6*4 activity to assess liver cirrhosis remains uncertain ***(Carcillo et al., 2013).***

Aim of the Work

The aim of this work is to detect the association between Cytochrome CYP2D6*4 genotype and liver cirrhosis. And to evaluate its clinical utility for screening of cirrhosis.

Liver Cirrhosis

I-Definition:

Cirrhosis is defined as a chronic degenerative disease in which normal liver cells are damaged then replaced by scar tissue. Cirrhosis is characterized by the histological development of regenerative nodules surrounded by fibrous bands in response to chronic liver injury, that leads to portal hypertension and end stage liver disease. Clinically, cirrhosis has been regarded as an end stage disease that invariably leads to death, unless liver transplantation is done, and the only preventive strategies have been screening for oesophageal varices and hepatocellular carcinoma ***(Serpaggi et al., 2006).***

II-Epidemiology:

The burden of liver cirrhosis in Egypt is exceptionally high, maintaining the highest prevalence of hepatitis C virus (HCV) worldwide. Liver cirrhosis represents a major cause of morbidity and mortality worldwide. The World Health Organization (WHO) estimates that in 2008 cirrhosis and primary liver cancer caused 783,000 and 619,000 deaths, respectively. Taken together, these