بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

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MONA MAGHRABY

Study of the Effect of CYP3A5 Single Nucleotide Polymorphism on Tacrolimus Metabolism in Liver Transplant Patients

Thesis

For Partial Fulfillment of Master Degree
in **Clinical Pathology**

By

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بسم الله الرحمن الرحيم

قَالُوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم

صدق الله العظيم

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Dina Ayed Abd ElMoez Habib

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List of Abbreviations

Abb.	Full term
ABCB1	ATP binding cassette subfamily B1
AP- 1	Activator protein 1
APC	Antigen-presenting cell
BCG	Bromocresol Green
CBC	Complete blood count
CCA	Cholangiocarcinoma
CMIA	Chemiluminescent Micro particle Immuno- Assay
CMIA	Chemiluminescent microparticle immunoassay
CMV	Cytomegalovirus
CNIs	Calcineurin inhibitors
CRF	Chronic renal failure
Cs	Cyclosporine
CYP	Cytochrome P450
DHPLC	Denaturing high-performance liquid chromatography
dNTP	Deoxyribonucleotide triphosphate
ELISA	Enzyme-linked immunosorbent assay
EMIT	Enzyme multiplied immunoassay technique
FAM	Fluorescein amidites
FKBP	FK binding protein
FRET	Fluorescence resonance energy transfer
HBV	Hepatitis B virus
HSV	Herpes simplex virus
ICU	Intensive Care Unit

List of Abbreviations (Cont...)

Abb.	Full term
IL-2	interleukin-2
IL-2Ra	Interleukin 2 receptor antagonists
INR	International normalized ratio
IQR	Inter-quartile range
JAK	Janus kinases
LC	Liquid chromatography- Mass spectrometry
LDH	Lactate dehydrogenase
LDLT	Living donor liver transplantation
LFA-1	Lymphocyte function-associated antigen 1
MBs	Molecular beacons
MDH	Malate dehydrogenase
MEIA	Microparticle enzyme-linked immuno-assay method
MELD	Model for End-stage Liver Disease score
MFOs	Mixed function oxidases
MHC	Major histocompatibility complex
MPAs	Mycophenolic acids
NAD	Nicotinamide adenine dinucleotide
NF-AT	Nuclear factor of activated T cells
NFQ	A non-fluorescent quencher
NF-κB	Nuclear factor
OLT	Orthotopic liver transplantation
PCR-RFLP	Polymerase chain reaction-restriction fragment length polymorphism
PML	Progressive multifocal leukoencephalopathy
PSMOs	Polysubstrate monooxygenases
PTLD	Post- transplant lymphoproliferative disorder
qPCR	Quantitative PCR

List of Abbreviations (Cont…)

Abb.	Full term
RIA	Radioimmunoassay
RT-PCR	Real Time- polymerase chain reaction technique
SNPs	single nucleotide polymorphisms
STAT	Signal transducers and activators of transcription
TDM	Therapeutic Drug Monitoring
TGF-β	Transforming growth factor-β
VLA-4	Very Late Antigen-4
WB I	Wash Buffer I
WB II	Wash Buffer II

INTRODUCTION

In Egypt, there is no doubt that chronic liver diseases are a major health concern.The high prevalence of hepatitis C virus that is estimated to be 14.7% and the high prevalence of chronic liver diseases has led to increasing numbers of patients suffering from end stage liver disease, necessitating liver transplantation, so living donor liver transplantation are now routinely done in Egypt in an increasing numbers *(Khaled and Ibrahim, 2016).*

Recent studies showed that 32.8% of de novo adult recipients of living donor liver transplantation (LDLT) experienced acute cellular rejection within the first 4 weeks after transplantation, so immunosuppressive agents are used post-operative to prevent rejection. Calcineurin inhibitors as Tacrolimus are the principal choice, prescribed to nearly 97% of liver transplanted patients *(Eunhee et al., 2018).* Tacrolimus has a narrow therapeutic window and large variability in pharmacokinetics, particularly during the early posttransplant period, therefore to overcome this variability and to optimize the efficacy and minimize the toxicity, therapeutic drug monitoring of tacrolimus is widely performed *(Shuker et al., 2015).*

A number of factors influence the pharmacokinetics of tacrolimus, including time after transplant, patient demographics, comorbidities and the patient and donor genotypes associated