بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

MONA MAGHRABY

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

MONA MAGHRABY

Role of Nucleotide Polymorphism in TLL1 Gene in Development of Hepatocellular Carcinoma in Patients Achieving Sustained Virological Response after Direct Acting Antiviral Drugs for HCV

Thesis

Submitted for Partial Fulfillment of

Doctorate Degree in **Tropical Medicine**

By

Ahmed Sayed Shahat Mohamed

MS.c Degree in Tropical Medicine, Ain Shams University

Under Supervision of

Prof. Dr. Soheir Abdelkader Elsayed

Professor of Tropical Medicine

Faculty of Medicine, Ain Shams University

Prof. Ashraf Mohamed Elbreedy

Assistant Professor of Tropical Medicine

Faculty of Medicine, Ain Shams University

Dr. Ahmed Hussein abd elhamid Elgazar

Lecturer of Tropical Medicine

Faculty of Medicine, Ain Shams University

Dr. Manar Mohamed Salah-Eldin

Lecturer of Tropical Medicine

Faculty of Medicine, Ain Shams University

Dr. Sarah Hasan A. Agwa

Assistant Consultant of Clinical Pathology and Molecular Biology, Medical Ain Shams Research Institute (MASRI)

Faculty of Medicine, Ain Shams University

2021

سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Soheir Abdelkader Elsayed****, Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University, for her meticulous supervision, kind guidance, valuable instructions and generous help.*

I am deeply thankful to ***Ass. Prof. Dr. Ashraf Mohamed Elbreedy****, Assistant Professor of Tropical Medicine, Faculty of Medicine, Ain Shams University, for his great help, outstanding support, active participation and guidance.*

Special thanks are due to ***Dr. Ahmed Hussein Elgazar****, Lecturer of Tropical Medicine, Faculty of Medicine, Ain Shams University, for his sincere efforts, fruitful encouragement.*

Thanks to ***Dr. Karim Abdel Aziz****, Lecturer of Tropical Medicine, Faculty of Medicine, Ain Shams University, for his great help, supervision and active guidance.*

Really I can hardly find the words to express my gratitude to ***Dr. Manar Mohamed Salah-Eldin****, Lecturer of Tropical Medicine, Faculty of Medicine, Ain Shams University, for his supervision, continuous help, and encouragement throughout this work.*

I want to express my gratitude to ***Dr. Sarah Hasan A. Agwa****, Assistant Consultant of Clinical Pathology and Molecular Biology, Medical, Ain Shams Research Institute (MASRI), for his supervision and tremendous effort, she has done in the meticulous revision of the whole laboratory work.*

I would like to express my hearty thanks to all my family for their support till this work was completed.

Ahmed Sayed Shahat Mohamed

List of Contents

List of Tables

List of Tables cont...

Table No.	Title	Page No.

List of Figures

List of Abbreviations

Abb.	Full term
aCL	*Anticardiolipin*
AFP	*Alpha-fetoprotein*
ALT	*Alanine aminotransferase*
Anti-SSA; SSA	*Anti-Sjögren Syndrome A*
Anti-SSB; SSB	*Anti-Sjögren Syndrome B*
APRI	*Aspartate aminotransferase -to-platelet ratio index*
AST	*Aspartate aminotransferase*
BCLC	*Barcelona Clinic Liver Cancer*
BCS	*Budd-Chiari syndrome*
BMP1/TLD	*Bone morphogenetic protein 1/tolloid*
CHC	*Chronic hepatitis C*
CLIP	*Cancer of the Liver Italian Program*
CT	*Computed tomography*
CTP	*Child-Turcotte-Pugh*
DAA	*Direct acting antiviral drugs*
DACLA	*Daclatasvir*
DHS	*Demographic Health Surveys*
DNA	*Deoxyribonucleic acid*
EASL	*European Association for the Study of the Liver*
ECM	*Extracellular matrix*
ECOG	*Eastern Cooperative Oncology Group*
EHIS	*Egyptian Health issues Survey*
FIB-4	*Fibrosis-4 Index*
GWAS	*Genome-wide association study*
HBV	*Hepatitis B virus*
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis C virus*
HR	*Hazard ratio*
HS	*Highly significant*
HSCs	*Human hepatic stellate cells*
HV	*Hepatic vein*

List of Abbreviations cont...

Abb.	Full term

IFN .....*Interferon*
INR .....*International normalized ratio*
IQR .....*Interquartile range*
IR .....*Insulin resistance*
IVC .....*Inferior vena cava*
kPa.....*Kilopascal*
LF .....*Liver fibrosis*
lncRNAs .....*Long non-coding RNA*
LR .....*Liver resection*
LT .....*Liver transplantation*
MASRI .....*Medical Ain Shams research Institute*
MC .....*Mixed cryoglobulinemia*
MELD Score.....*Model for End-Stage Liver Disease*
MoH.....*Ministry of health*
MRI .....*Magnetic resonance imaging*
mRNA .....*Messenger RNA*
mTLL1.....*Mammalian Tolloid-like 1*
MWA .....*Microwave ablation*
NAFLD .....*Nonalcoholic fatty liver disease*
NCCVH .....*National Committee for Control of Viral Hepatitis in Egypt*
NHL .....*Hodgkin lymphoma*
NK .....*Natural killer*
NS .....*Non significant*
P .....*P value*
PAN .....*Polyarteritisnodosa*
PBC.....*Primary biliary cirrhosis*
PCR .....*Polymerase chain reaction*
PEI .....*Percutaneous ethanol injection*
PHT .....*Portal hypertension*
PSC.....*Primary sclerosing cholangitis*
PWID .....*Persons Who Inject Drugs*
RF.....*Rheumatoid factor*

List of Abbreviations cont...

Abb.	Full term

RIBA .....*Ribavirin*
RNA .....*Ribonucleic acid*
S .....*Significant*
SD .....*Standard deviation*
SNP .....*Single Nucleotide Polymorphism*
SOF .....*Sofosbuvir*
SPSS .....*Statistical package for Social Science*
SVR .....*Sustained virological response*
T2DM.....*Type 2 Diabetes*
TACE .....*Trans arterial chemoembolization*
TARE .....*Trans arterial Radioembolization*
TGF-β .....*Transforming growth factor beta*
TLL1.....*TolloidLike 1 Gene*
TNM .....*Tumour, Node and Metastases*
ULN .....*Upper limit of normal*
UTRs .....*Untranslated regions*
VEGF .....*Vascular growth factor*

INTRODUCTION

Incidence of Hepatocellular carcinoma (HCC) has rapidly increased world wide. HCC is the sixth most common malignancy and the third most common cause of cancer related death ***(Kadalayil et al., 2013).*** In Egypt, liver cancer forms 23.81% of the total malignancies. HCC constitutes 70.48% of all liver Tumours among Egyptians ***(Forner et al., 2012).*** Recent investigations in Egypt have shown the increasing importance of HCV infection in the etiology of liver cancer, estimated to account for 40–50% of cases ***(Shaker et al., 2013).***

Chronic infection with hepatitis C virus (HCV) is the leading cause of end-stage liver disease, HCC and liver-related death in Egypt. HCV causes chronic hepatitis in 60%–80% of the patients, and 10%–20% of those patients develop cirrhosis over 20–30 years of HCV infection. About 1%–5% of the patients with liver cirrhosis may develop HCC and 3%–6% may decompensate during the following 20–30 years. The risk of death in the following year after an episode of decompensation is between 15% and 20% ***(Westbrook et al., 2015).***

Direct-acting antiviral agents (DAA) for chronic hepatitis C have initiated a revolution in the management and control of this important liver disease with cure rates over 90**%** ***(AASLD/IDSA Hepatitis C guidance, 2015; Conti et al., 2016).***

The ease of administration, short duration of treatment, excellent tolerance and absence of severe side effects have made therapy of hepatitis C appropriate to all patients with chronic hepatitis C with different stages of disease severity ***(Hoofnagle et al., 2016).*** Highly effective DAA were expected to dramatically decrease HCV related liver disease progression to end-stage liver disease and HCC ***(Foster et al., 2016).***

In fact, the risk of developing HCC continues to persist in those patients with HCV cirrhosis even after they have achieved SVR ***(Brown et al., 2016)***. However, it has been suggested that HCC may occur or recur in patients with chronic HCV infection who received DAA therapy. Because this phenomenon was not seen in patients treated with interferon or ribavirin, some experts speculate that these novel DAA may in fact play a significant role in Tumour development ***(Foster et al., 2016).*** However, data on HCC risk following DAA are still sparse and conflicting ***(El-serag et al., 2016).***

For decades of years, there were a lot of studies have explored the relationship of polymorphisms of candidate gene and HCC. Single Nucleotide Polymorphism (SNP) a genetic polymorphism between two genomes that is based on deletion, insertion, or exchange of a single nucleotide.

It is assumed that a decreased ability to eliminate cells with DNA damage may facilitate the accumulation of somatic mutations, and thereby contribute to Tumour initiation,