Impact of the type of Human Leucocyte Antigen – A Allele on the Outcome of Hepatitis C Virus Infection in the Egyptian Population

Thesis

Submitted for Partial Fulfillment of MD in Clinical and Chemical Pathology

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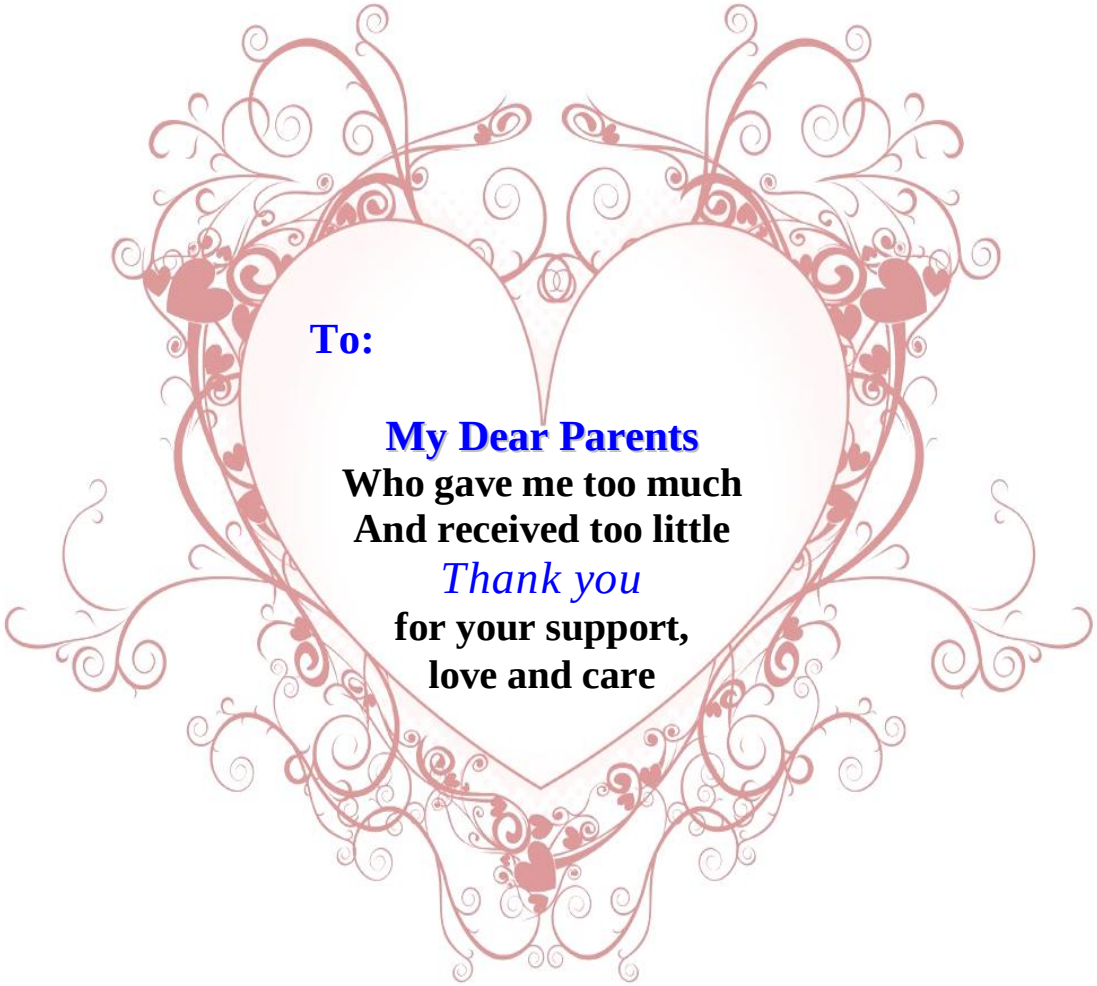
2013



To:

My Dear Parents
Who gave me too much
And received too little
Thank you
for your support,
love and care

Acknowledgement

First and foremost, Thanks are given to God, the source of all knowledge, by whose abundant aid this work has come to fruition.

It has been a great honor to proceed this work under the supervision of Professor/ Aisha Yassin Abdel-Ghaffar, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University. I will never forget her unlimited help, kind encouragement and wise guidance. To her, words of praise are not sufficient and I am really greatly indebted to her.

I would like also to express my sincere gratitude and appreciation to Professor/ Nahla Mohamed Zakaria Yousef, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her enthusiastic guidance, unique effort, valuable advice and generous help throughout this work.

I pay my profound thanks to Assistant Professor/ Amal Ahmed Abbas, Assistant professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her enlightening supervision and guidance with valuable comments.

Special thanks to Assistant Professor / Dina El-Sayed El-Shennawy, Assistant professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for her useful assistance and helpful supervision throughout this work.

Last but not least my sincere thanks and appreciation to ***Dr. Dina Ali & Dr. Waleed Abdelhady*** *for their cooperation and profound help in this study.*

This thesis was supported by the ***STDF*** *grant number 457.*

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List of Abbreviations

Abb.	Full term
7meG	*7-methylguanosine*
aa	*Amino acid*
AIDS	*Acquired immunodeficiency syndrome*
ALT	*Alanine transaminase*
APCs	*Antigen presenting cells*
ARF	*Alternate reading frame*
ATPase	*Adenosine Triphosphatase*
BLyS	*B-lymphocyte stimulator*
bp	*Base pairs*
CD	*Cluster of differentiation*
CDC	*Complement dependant microlymphocytotoxicity*
cDNA	*Complementary DNA*
CLDN	*Claudin*
CREG	*Cross Reacting Group*
CTLs	*Cytotoxic T-lymphocytes*
DAA	*Direct antiviral agents*
dATP	*Deoxyadenosine triphosphate*
DC	*Dendritic cell*
dCTP	*Deoxycytidine triphosphate*
ddATP	*Dideoxyadenosine triphosphate*
ddCTP	*Deoxycytidine triphosphate*
ddGTP	*Dideoxyguanosine triphosphate*
ddTTP	*Dideoxythymidine triphosphate*
DGGE	*Denaturing gradient gel electrophoresis*
dGTP	*Deoxyguanosine triphosphate*
DNA	*Deoxyribonucleic acid*
dsRNA	*Double stranded RNA*
dTTP	*Deoxythymidine triphosphate*
E	*Envelope*
EHMs	*Extrahepatic manifestations*
eIF2	*Eukaryotic Initiation Factor 2*

ER	*Endoplasmic reticulum*
ERAP	*ER-resident aminopeptidase*
F	*Frameshift*
Foxp3	*Forkhead box P3*
GAGs	*Glycosaminoglycans*
GN	*Glomerulonephritis*
GWAS	*Genome-wide association studies*
H^+	*Hydrogen ion*
HBV	*Hepatitis B virus*
HCC	*Hepatocellular carcinoma*
HCV	*Hepatitis C virus*
HCV-LPs	*HCV-like particles*
HDL	*High density lipoprotein*
HIV	*Human immunodeficiency virus*
HLA	*Human leukocyte antigens*
HPV	*Human papilloma virus*
hsp	*Heat shock protein*
HVR	*Hypervariable regions*
IDDM	*Insulin dependant diabetes mellitus*
IDU	*Injection drug use*
IFN	*Interferon*
Igs	*Immunoglobulins*
IL	*Interleukin*
IL-2Rα	*IL-2 receptor α*
IP-10	*INF-γ-inducible protein 10*
IRES	*Internal ribosome entry side*
IRF3	*IFN regulatory factor 3*
ISDR	*IFN-α sensitivity-determining region*
ITIM	*Immunoreceptor tyrosine-based inhibitory motif*
IU/L	*International unit/Litre*
IU/ml	*International unit/millilitre*
JAK	*Janus kinase*
kb	*kilobase*
kDa	*kilodalton*
KIR	*Killer immunoglobulin-like receptor*
LD	*Linkage disequilibrium*
LDL	*Low density lipoprotein*
LDL-R	*LDL-receptor*

LKM	*Liver-kidney microsomal*
LTA	*Lymphotoxin alpha*
LTB	*Lymphotoxin beta*
Mbp	*Mega basepair*
MHC	*Major histocompatibility complex*
MICA	*Major histocompatibility complex class I–related chain A*
miRNA	*MicroRNA*
MLC	*Mixed lymphocyte culture*
mRNA	*Messenger RNA*
MS	*Multiple sclerosis*
NF-κB	*Nuclear factor kappa B*
NHL	*Non-Hodgkin's lymphoma*
NK	*Natural killer*
NKT	*Natural killer T cell*
NS	*Non Structural*
NTPase	*Nucleoside triphosphatase*
OCLN	*Occludin*
ORF	*Open reading frame*
PBMCs	*Peripheral blood mononuclear cells*
PCR	*Polymerase chain reaction*
PD-1	*Programmed cell death protein 1*
PD-L1	*PD-1 ligand*
PKR	*Protein kinase RNA-activated*
RA	*Rheumatoid arthritis*
RC	*Replication complex*
RdRp	*RNA-dependent RNA polymerase*
RF	*Rheumatoid factor*
RFLP	*Restriction fragment length polymorphism*
RIG-I	*Retinoic acid–inducible gene I*
RNA	*Ribonucleic acid*
ROS	*Reactive oxygen species*
SL	*Stem-loop*
SLE	*Systemic lupus erythematosus*
SNPs	*Single nucleotide polymorphisms*
SR-BI	*Scavenger receptor class B type I*
SSCP	*Single strand conformation polymorphism*
SSOP	*Sequence specific oligonucleotide probe/probing*

SSP	*Sequence specific primer/priming*
STAT	*Signal transducer and activator of transcription*
SVR	*Sustained virologic response*
TAP	*Transporter protein*
Taq	*Thermus aquaticus*
TCRs	*T-cell receptor*
TGF	*Transforming growth factor*
TGGE	*Temperature gradient gel electrophoresis*
Th	*T helper*
TLR3	*Toll like receptor 3*
TNF-α	*Tumor necrosis factor alpha*
Tregs	*Regulatory T cells*
U/UC	*Polyuridine polypyrimidine*
UTR	*Untranslated region*
VLDL	*Very low density lipoprotein*
WHO	*World Health Organization*
α	*Alpha*
β	*Beta*
λ	*Delta*

INTRODUCTION

Hepatitis C virus (HCV) was identified and cloned in 1989. It is estimated that more than 170 million persons are infected with HCV world-wide (3% of population) and as many as 3 million individuals are newly infected each year. In 20–30% of infections the virus is cleared spontaneously; however, in the majority of patients the virus persists. The mechanism by which some individuals spontaneously resolve infection, while others become chronically infected is not clearly understood **(Edwards et al., 2012)**. Both virus-related factors such as viral heterogeneity and replicative activity and the host determinants such as lack of efficient immune responses are involved in the pathogenesis of chronic hepatitis **(Tripathy et al., 2009)**.

The most striking features of HCV are its propensity to persist in a large proportion of infected individuals and the broad spectrum of liver disease that result from infection. Currently, there is no available vaccine to prevent HCV infection **(Obeid, 2011)**. Studies in humans and animal models of HCV infection have demonstrated that HCV elicits innate immune responses early after infection. However, the virus can persist in the face of the innate immune response. Indeed, viral clearance occurs only in the presence of antiviral $CD4^+$ and $CD8^+$ T cell responses **(Dustin and Rice, 2007)**.

A successful T cell response requires the presentation of viral peptides bound to HLA molecules on the surface of