

**Evaluation of the role of different  
Apolipoprotein-E genotypes in the outcome  
of liver disease caused by Hepatitis C virus**

**Thesis**

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# LIST OF ABBREVIATIONS

<b>AD</b>	Alzheimer's Disease
<b>AFP</b>	Alpha-Fetoprotein
<b>AIDS</b>	Acquired Immunodeficiency Syndrome
<b>ALT</b>	Alanine Transaminase
<b>ANOVA</b>	Analysis Of Variance
<b>ASO</b>	Allele-Specific Oligonucleotides
<b>AST</b>	Aspartate Transaminase
<b>ApoE</b>	Apolipoprotein-E
<b>Bp</b>	Base Pairs
<b>BUN</b>	Blood Urea Nitrogen
<b>CBC</b>	Complete Blood Count
<b>CDC</b>	Centers for Disease Control and Prevention
<b>CM</b>	Chylomicrons
<b>CNS</b>	Central Nervous System
<b>CVD</b>	Cardiovascular Disease
<b>DNA</b>	Deoxyribonucleic acid
<b>EDTA</b>	Ethylene-Diamine-Tetraacetic Acid
<b>ELISA</b>	Enzyme-Linked Immunosorbant Assay
<b>ER</b>	Endoplasmic Reticulum
<b>ESLD</b>	End-Stage Liver Disease

<b>Hb</b>	Hemoglobin
<b>HBV</b>	Hepatitis B Virus
<b>HCC</b>	Hepatocellular Carcinoma
<b>HCV</b>	Hepatitis C Virus
<b>HDL</b>	High Density Lipoproteins
<b>HFL</b>	Hepatic Focal Lesion
<b>HIV-1</b>	Human Immunodeficiency Virus 1
<b>HLA</b>	Human Leukocyte Antigen
<b>HSPG</b>	Heparin Sulfate Proteoglycans
<b>HSV</b>	Herpes Simplex Virus
<b>HVAP-A</b>	Human VAMP-Associated Protein A
<b>HVR1</b>	Hypervariable Region 1
<b>IDL</b>	Intermediate Density Lipoprotein
<b>IL-2</b>	Interleukin 2
<b>iNOS</b>	Inducible Nitric Oxide Synthase
<b>INR</b>	International Normalization Ratio
<b>IRES</b>	Internal Ribosomal Entry Site
<b>LDL</b>	Low Density Lipoproteins
<b>LDLRs</b>	Low Density Lipoprotein Receptors
<b>LRP</b>	LDL Receptor-Related Protein
<b>LVP</b>	Lipo-Viro Particle

<b>MELD</b>	Model of End-Stage Liver Disease
<b>MPGN</b>	Membranoproliferative Glomerulonephritis
<b>mRNA</b>	Messenger Ribonucleic Acid
<b>NASH</b>	Non-Alcoholic Steatohepatitis
<b>NHANES</b>	National Health and Nutrition Examination Survey
<b>NIH</b>	National Institutes of Health in the United States
<b>NS</b>	Non-Structural
<b>OR</b>	Odds Ratio
<b>PBMCs</b>	Peripheral Blood Mononuclear Cells
<b>PBS</b>	Phosphate Buffer Saline
<b>PCR</b>	Polymerase Chain Reaction
<b>PLT</b>	Platelets
<b>PT</b>	Prothrombin Time
<b>PTT</b>	Partial Thromboplastin Time
<b>RDRP</b>	RNA-Dependent RNA Polymerase
<b>RNA</b>	Ribonucleic Acid
<b>SD</b>	Standard Deviation
<b>SPSS</b>	Statistical Package for Special Science
<b>SR-BI</b>	Scavenger Receptor Class B Type I
<b>SVR</b>	Sustained Viral Response
<b>Tat</b>	Transactivator Protein

<b>TGFβ1</b>	Transforming Growth Factor β1
<b>TLC</b>	Total Leukocytic Count
<b>TNF-A</b>	Tumour Necrosis Factor A
<b>UTR</b>	Untranslated Region
<b>UV</b>	Ultraviolet
<b>VAMP</b>	Vesicle-Associated Membrane Protein
<b>VLDL</b>	Very Low Density Lipoproteins

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## INTRODUCTION

Hepatitis C virus (HCV) infection is a major global health problem. More than 170 million people worldwide are infected with HCV (*Poynard et al., 2003, Shepard et al., 2005, Kamal and Nasser, 2008*). HCV is a causative agent of chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC) (*Hishiki et al., 2010*). In Egypt, HCV prevalence is ~15%, which is considered the highest prevalence worldwide, with genotype 4 being the most common, and responsible for 90% of HCV infections in Egypt (*Egyptian Ministry of Health, 2007, Kamal and Nasser, 2008, El-Zanaty and Ann Way., 2009*).

There are several possible outcomes after infection with HCV (*Alter et al., 1992*). Approximately 15% to 20% of infected individuals clear the virus, as evidenced by the presence of anti-HCV antibodies, but absence of viral RNA in serum. The remaining individuals (~85%) become chronically infected, with HCV RNA readily detectable in serum (*Seeff and Hoofnagle, 2002*).

The consequences of chronic infection also vary: some individuals develop minor or no liver damage, whereas others suffer from progressive chronic hepatitis, leading to liver cirrhosis, and even HCC. The reasons for the diversity of outcomes of HCV infection are still unclear.

At least 6 major HCV genotypes are identified (*Robertson et al., 1998, NIH Consensus State Sci Statements, 2002*). However, infection with a particular genotype is not thought to influence disease outcome (*Alric et al., 2000*). Alternatively, host factors may be important. Some factors include male sex, an older age at

infection, increased alcohol intake, coinfection with Human Immunodeficiency Virus 1 (HIV-1) or Hepatitis B virus (HBV), and insulin resistance (*Sanchez-Quijano et al., 1995, Poynard et al., 1997, Wiley et al., 1998, Zarski et al., 1998, Mohsen and the Trent HCV Study Group, 2001, Sud et al., 2004, Price et al., 2006*).

HCV particles circulating in the blood of HCV carriers associate with lipoproteins, such as low-density lipoproteins (LDL), very low density lipoproteins (VLDL) and chylomicrons (CM); thus, it is termed a lipo-viro particle (LVP) (*Andre et al., 2002, Nielsen et al., 2006, Hishiki et al., 2010*).

It has been suggested that the virus might gain entry into cells via a hitchhiker method with the lipoproteins (*Agnello V et al., 1999*). Specifically, entry might involve LDL receptors (LDLRs) (*Price et al., 2006*). One of the trials that supported this theory was done using COS-7 cells, which are fibroblast-like cells derived from monkeys kidney tissue and used in production of different recombinant proteins. These cells were transfected with the human gene for LDLR, and were found to bind more HCV particles than untransfected cells. Another trial used antibodies that block binding of ligands to LDLRs, and it was found that they also block binding of HCV to cells (*Monazahian M et al., 1999*). The virus also has been shown to bind directly to certain apolipoproteins, which might facilitate entry (*Depla E et al., 1998, Sabile A et al., 1999*).

Several lipoproteins groups contain Apolipoprotein-E (ApoE), a polymorphic and multifunctional protein with numerous roles in lipoproteins metabolism. The three common isoforms: ApoE2, ApoE3 and ApoE4 show isoform-specific functional properties