The Relationship between IL28B Genotypes and Hepatoma in Post HCV Cirrhotic Patients

Thesis

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Mohamed Taha Abd EL Gawad

Index

Page

List of Tables

List of Figures and Diagrams

List of Abbreviation

5-HT1A .....5-hydroxytryptamine receptor 1A

AASLD ..... American Association for the study of liver disease

AAT..... Alpha 1-antitrypsin deficiency

AFP ..... Alphafetoprotein

ALD..... Alcoholic liver disease

ALP ..... Alkaline phosphatase

ALT..... Alanine aminotransferase

APRI ..... Aspartate aminotransferase/platelet ratio

AST ..... Aspartate aminotransferase

AT1 ..... Angiotensin receptor 1

AUROC..... Area under receiver operating characteristics

Bcl-2 .....B-cell lymphoma 2

BCLC ..... Barcelona Clinic Liver Cancer

BM..... Bone marrow

BMI ..... Body mass index

BUN..... Blood Urea Nitrogen

CB1 ..... Cannabinoid receptor 1

CD 14 ..... Cluster of differentiation 14

CHC ..... Chronic Hepatitis C Virus

CLIP..... Cancer of the Liver Italian Program scoring system

CPT ..... Child-Pugh-Turcotte

CRS7 ..... Cirrhosis risk score 7

CT ..... Computed tomography

DDX5 .....DEAD box protein 5

DEPDC5.....DEP domain-containing 5

DLD..... Decompensated liver disease

DNA ..... Deoxyribonucleic acid

EASL..... European Association For The Study Of The Liver

ECM..... Extra cellular matrix

EDHS ..... Egyptian Demographic Health Survey

EGF..... Epidermal growth factor

ELF ..... Enhanced liver fibrosis

EMT..... Epithelial-mesenchymal transition

ESLD..... End stage Liver Disease

EVR..... Early virological response

GGT ..... Gamma glutamyl tranferase

GSTM1 ..... Glutathione S-transferase mu 1

GSTT1 ..... Glutathione S-transferase theta 1

GWAS..... Genome-wide association studies

HALTC..... Hepatitis C Antiviral Long-term Treatment against Cirrhosis cohort

HAV ..... Hepatitis A virus

HbeAg ..... Hepatitis B E antigen

HbsAg ..... Hepatitis B Surface Antigen

HBV DNA..... Hepatitis B Deoxyribonucleic acid

HBV ..... Hepatitis B virus

HCC ..... Hepatocellular carcinoma

HCV ..... Hepatitis C virus

HFE..... Hemochromatosis

HIV ..... Human immunodeficiency virus

HSCs ..... Hepatic Stellate Cells

IASL..... International Association for the Study of the Liver

IFN k..... Interferon kappa

IFN α..... Interferon alpha

IFN λ..... Interferon lambda

IFN ..... Interferon

IgG ..... Immune globulins **G**

IL10..... Interleukin 10

IL28B ..... Interleukin 28B

IL29..... Interleukin 29

IL-6 ..... Interleukin 6

INR..... International normalized ratio

ISG ..... Interferon -stimulating genes

JAK-STAT.... Janus kinase–signal transducers and activators of transcription signaling cascade

KPa .....kilo Pascal

LAL..... Lysosomal acid lipase deficiency

LBP ..... Elevated binding protein

LCT..... Liver cell transplantation

LFTs..... Liver function tests

LOXL2..... Enzyme Lysil oxidase-like-2

LPS.....Lipopolysaccharide

LT.....Liver transplantation

MDCT.....Multidetector CT

MDM2.....Mouse double minute 2 homolog

MELD.....Model for End-StageLiver Disease

MICA.....The human major histocompatibility complex class I chain-related gene A

MiRs.....MicroRNAs

MMP.....Matrix metalloproteinases

MRI.....Magnetic resonance imaging

MSCs.....Mesenchymal stem cells serve

NAFLD.....Non-alcoholic Fatty Liver Disease

NASH.....Non-alcoholic steatohepatitis

NIHC.....NIHConsensusStatement on Management of Hepatitis C

NK.....Natural killer

NKT.....Natural killer T cell

NTR.....Nontranslated regions

p53.....Tumor protein53

PBC.....Primary biliary cirrhosis

PCR.....Polymerase chain reaction

PEG-IFN.....Pegylated Interferon

PELD.....Pediatric End-Stage Liver Disease

PSC.....Primary sclerosing cholangitis

PT.....Prothrombin Time

RAS.....Renin angiotensin pathway

RBV.....Ribavirin

RCT.....Randomized controlled trial

RFA.....Radiofrequency ablation

RNA .....Ribonucleic acid Of Hepatitis C Virus

RVR .....Rapid virological response

SNPs.....Single nucleotide polymorphisms

SPSS.....Statistical package for social science

STAT-C .....Specifically Targeted Antiviral Therapy for HCV

SVR.....Sustained virological response

TACE.....Transarterial chemoembolization

TE.....Transient Elastography

TGF β1 .....Transforming Growth Factor Beta 1 receptor

TIMP.....Tissue inhibitors of matrix metalloproteinase

TLR.....Toll-like receptor pathway

TNFR-1.....Tumor Necrosing Factor alpha 1 Receptors

TNM.....Tumor, node, and metastases staging system

U/S.....Ultra Sound

USA.....United states of America

UTRs.....Untranslated regions

VEGF.....Vascular endothelial growth factor

WHO.....World Health Organization

XPC.....Xeroderma pigmentosum, complementation group C

ABSTRACT

Background: Egypt has the highest prevalence of HCV worldwide 13.8 %.Over the past couple of years there has been a lot of studies supporting the role of IL28b in treatment response of HCV infected patients who are receiving interferon therapy. Il28b is a cytokine that belongs to the interferon IFN-lambda (type-III IFN) family. Il28b has 3 subtypes (CC, CT, TT): the treatment response to pegylated interferon with ribavirin has shown to differ according to the subtype present in each patient. 10% -20% of those who are chronically infected with chronic hepatitis C will progress to cirrhosis and 5% will develop hepatocellular carcinoma. Hepatocellular carcinoma (HCC) comprises nearly 6% of all incident cancer cases worldwide. (HCC) is the 3rd most frequent cause of the cancer mortality among men world wide. HCC) is the 2nd most frequent cause of cancer incidence and mortality among men in Egypt. Liver carcinogenesis is a complex and multi-factorial process, in which both environmental and genetic features interfere and contribute to malignant transformation. IL-28B rs12979860 (C/T) polymorphism and the (T/T) allele appears to be more prevalent in patients with ESLD (LC and HCC) (hepatoma & liver cell failure). Besides, the C/C genotype is protective against the development of chronic HCV infection as well as later at the final stages of the disease

Objective: The objective of the study is to determine a simple and easy test that can be applied to predict occurrence of hepatoma in post HCV cirrhotic patients. The aim of the study is to find a correlation between to determine the relationship between different types of (SNPs) Single- nucleotide polymorphisms of IL-28B gene and hepatoma in child B and C cirrhotic patients infected by hepatitis c genotype 4.

Methods: This study was conducted on 40 post HCV cirrhotic patients genotype (4) who were classified into:

- Group (1) 20 cirrhotic patients with Hepatoma
- Group (2) 20 cirrhotic patients without Hepatoma attended (Ain Shams university Hospital).
- IL28B genotyping by **Taq Man® Real- Time PCR** was done t o all patients during the follow up visits to detect the type of IL28B polymorphism.

Results: As regard gene polymorphism, it was CC in 11 cases (27.5%), CT in 10 cases (25.0%) and TT in 19 cases (47.5%) and there was non-significant difference between group 1 and group 2; In group 1, the distribution was CC, CT and TT in 15.0%, 30.0% and 55.0% respectively; while in group 2, the distribution was CC, CT and TT in 40.0%, 20.0% and 40.0% respectively.

Conclusion: Our data suggest there is a relation between IL28B genotypes and development of hepatoma and hepatic decompensation.

Keywords: HCV, Cirrhosis, Hepatoma (H.C.C). IL28B.

INTRODUCTION

An estimated 270-300 million people worldwide are infected with hepatitis C. No vaccine against hepatitis C is currently available **(Houghton, 2009).**

Prevalence is higher in some countries in Africa and Asia. Egypt has the highest seroprevalence for HCV, up to 20% in some areas. There is a hypothesis that the high prevalence is linked to a now-discontinued mass-treatment campaign for schistosomiasis, which is endemic in that country. Regardless of how the epidemic started, a high rate of HCV transmission continues in Egypt, both iatrogenically and within the community and household **(Frank et al., 2000).**

For genotype 1 hepatitis C treated with pegylated interferon-alpha-2a or pegylated interferon-alpha-2b combined with ribavirin, it has been shown that genetic polymorphisms near the human IL28B gene, encoding interferon lambda 3, are associated with significant differences in response to the treatment. This finding, originally reported in Nature, showed that genotype 1 hepatitis C patients carrying certain genetic variant alleles near the IL28B gene are more possibly to achieve sustained virological response after the treatment than others. A later report from Nature demonstrated the same genetic variants are also associated with the natural clearance of the genotype 1 hepatitis C virus ***(*Thomas et al., 2009).**

There is a relation between the gene Il28b and early virological response (EVR) with interferon based therapy in Egyptian patients infected by HCV genotype 4 (**Mohsen M. Maher et al., 2012).**

Hepatocellular carcinoma (HCC) comprises nearly 6% of all incident cancer cases worldwide. Which the overwhelming majority occurring in the developing world.one of the least curable malignancies. (HCC) is the 3rd most frequent cause of the cancer mortality among men world wide. chronic infection with hepatitis be virus (HBV) and he patitis C virus (HCV) have been cited as. by far the most important etiologic agent according to the world health organization (WHO) 350 million people are chronically infected with (HBV) and (HCV). The relative importance of (HBV) and (HCV) as causative agent can vary greatly from region to region and over time incidence of (HCC). In Egypt currently increasing, which may be a result of a shift in the relative importance of (HCV) and (HBV) as primary risk factors. (HCC) is the 2nd most frequent cause of cancer incidence and mortality among men in Egypt. hospital based studies from Egypt have reported an increase in the relative frequent of liver-related cancers in Egypt › 95% as HCC from nearly 4% in 1993 to 7.3% in 2003 **(Lehman and Wilson et al., 2009).**

Liver carcinogenesis is a complex and multi-factorial process, in which both environmental and genetic features interfere and contribute to malignant transformation. Patients with cirrhosis are particularly exposed and justify periodical screenings in order to detect the early development of hepatocellular carcinoma (HCC). The risk of HCC is, however, not identical from one patient to another. The identification of host factors that may also play an important role in HCC development may improve our understanding of the implications of the various biological pathways involved in liver carcinogenesis; such progress may as well help refine the selection of patients who could benefit from specific preventative measures or could be given adapted screening policies **(Nahon and Zucman-Rossi, 2012).**