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Clinical Utility of CTNNB1 (c.121A>G) Mutation in Circulating Tumor DNA in Egyptian Patients with Hepatocellular Carcinoma: A Case-Control Study

Thesis

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List of Abbreviations

Abb.	Full term
AASLD:	*Association for the study of liver disease.*
AFP:	*Alpha - feto protein.*
AFPL3:	*Lens culinaris agglutinin reactive fraction of alpha fetoprotein.*
AICR:	*American institute for cancer research.*
AIDS:	*Acquired immune deficiency syndrome.*
AJCC:	*American joint committee on cancer.*
APHE:	*Arterial* phase hyperenhancement
ARHE:	*Arterial phase hyperenhancement.*
BCLC:	*Barcelona clinic liver cancer.*
CfDNA:	*Cell free DNA.*
CK19:	*Cytokeratin 19.*
CLIP:	*Cancer of the liver Italian program.*
CMH:	*Combined Military Hospital:*
CRPH:	*Clinically relevant portal hypertension.*
CSPH:	*Clinical significant portal hypertension.*
CTCs:	*Circulating tumor cells.*
CtDNA:	*Circulating tumor Deoxyribonucleic acid.*
DCP:	*Des gamma carboxy prothrombin.*
DEB:	*Drug eluting beads.*
DM:	*Diabetes Mellitus.*
EASL:	*European association for study of the liver.*
ECOG:	*Eastern cooperative oncology group.*
EORTC:	*European organization for research and treatment of cancer.*
ER:	*Endoplasmic reticulum.*
F18 FDG:	*Fludeoxyglucose F 18.*
FDA:	*Food and drug administration.*
FGF:	*Fibroblast growth factor.*
FGF314:	*Fibroblast growth factor 314.*

List of Abbreviations (Cont...)

Abb.	Full term
GP73:	*Golgi protein 73.*
GPC3:	*Glypican 3.*
GS:	*Glutamine synthase.*
GSk3:	*Glycogen synthase Kinase 3*
HBe Ag:	*Hepatitis B virus e antigen.*
HBS Ag:	*Hepatitis B surface antigen.*
HBV:	*Hepatitis B virus.*
HCC:	*Hepatoceullar carcinoma.*
HCV:	*Hepatitis C virus.*
HDV:	*Hepatitis D virus.*
HFE:	*Hemochromatosis gene.*
HH:	*Hereditary hemochromatosis.*
HIV:	*Human immunodeficiency virus.*
HSP70:	*Heat shock protein 70.*
HTN:	*Hypertension.*
HVPG:	*Hepatic venous pressure gradient.*
IARC:	*International Agency for research on cancer.*
IncRNAs:	*Long non coding ribonuclecic acid.*
KIT:	*Proto-oncogen receptor tyrosine kinase.*
LI-RADS:	*Liver Imaging Reporting and Data System*
lncRNA-UCA1:	*Long noncoding RNA–Urothelial Carcinoma Associated-1.*
lncRNA-WRAP53	*Long noncoding RNA– WD repeat containing, antisense to TP53.*
LSM:	*Liver stiffness measurement.*
LT:	*Liver transplantation.*
MDCT:	*Multidetector computed Tomography.*
MELD:	*Model for end stage liver disease.*
MiR503:	*Mir503 host gene.*

List of Abbreviations (Cont...)

Abb.	Full term
MiRNAs:	*Micro ribonucleic acid.*
MRI:	*Magnetic resonance imaging.*
MVI:	*Microvascular invasion.*
MWA:	*Microwave ablation.*
NAFLD:	*Non alcoholic fatty liver disease.*
NASH:	*Non alcoholic steatohepatitis.*
OLT :	*Orthotopic liver transplantation*
OPN:	*Osteopontin.*
PBC:	*Primary biliary cirrhosis.*
PDGF:	*Platelet derived growth factor.*
PET:	*Positron emission tomography.*
PIVKA II:	*Protein induced by vitamin K absence.*
PLA:	*Percutaneous laser ablation.*
PVA:	*Polyvinyl alcohol.*
PVT:	*Portal vein thrombosis.*
RET:	*Rearranged during transfection.*
RFA:	*Radiofrequency ablation.*
SCCA:	*Squamous cell carcinoma.*
TACE:	*Transarterial chemoembolization.*
TNM:	*Tumor –node- metastasis.*
TP53:	*Tumor protein p 53.*
TTP:	*Time to progression.*
UCSF:	*University of California, san fransisco.*
VEGF:	*Vascular endothelial growth factor.*
WCRF:	*World cancer research fund.*
WD:	*Wilson disease.*
α1AT:	*Alpha 1 antitrypsin.*

INTRODUCTION

Hepatocellular carcinoma (HCC) is a primary tumor of the liver. It constitutes about 90% of all primary liver cancers and usually develops in the setting of chronic liver disease, particularly in patients with chronic hepatitis B and C. In Egypt, HCC causes a significant public health problem with a rising incidence due to the strong link between HCC and the high prevalence of viral hepatitis and its complications mainly hepatitis C virus (HCV) ***(Tawfik et al., 2019; Yehia et al., 2020).*** Hepatocellular carcinoma (HCC) is the sixth and fourth common cancer worldwide and in Egypt respectively with Egypt ranking the third country in Africa ***(Rashed et al., 2020).***

According to the ***European Association for Study of the Liver (EASL) guidelines (2018)***, one of the unmet needs in HCC research is to develop non-invasive tools for early detection. Nevertheless, without a liver biopsy, assessment of the genomic profile becomes a challenge.

This can be addressed using non-invasive liquid biopsy which provides actionable genomic information without the risk of complications. Recently, circulating tumor DNA (ctDNA) has attracted extensive attention for its possible utility in cancer research. Circulating tumor DNA is mutant DNA released into the circulation by tumor cells and are a part of circulating cell-free DNA (cfDNA) and can be assessed through analysis of plasma from a blood sample of HCC

patient. In a liquid biopsy as a blood sample, ctDNA can be used to comprehensively profile the tumor genome better than conventional sampling methods. Thus, qualifying it as a better vehicle to provide information about abnormalities in genes for guiding targeted therapy, unveiling drug resistance, and monitoring treatment response ***(Morishita and Masaki, 2015).***

Over the past decade, advances in genomic research have increased our knowledge of HCC molecular pathogenesis. However, the exact molecular mechanisms underlying the development of HCC are still unclear. Among the molecular signaling pathways implicated in the pathogenesis of HCC is the Wnt/β-catenin signaling pathway. It is one of the most frequently activated pathways in up to 50% of HCC. Wnt/β-catenin signaling is a highly conserved pathway that regulates key cellular functions including; proliferation, differentiation, migration, genetic stability, apoptosis, and stem cell renewal. The Wnt pathway mediates biological processes depending on the involvement of β-catenin in signal transduction. Levels of β-catenin are low owing to the presence of β-catenin destruction complex (APC, axin, and GSK-3). Mutations can result in sustained aberrant activation of the Wnt/β-catenin pathway and thus dysregulate multiple cellular functions, including proliferation, apoptosis, and cell motility **(*Pai et al., 2017; Khalaf et al., 2018).***