
# *The Role of Aberrant Promoter Methylation in Chronic Liver Patients and Hepatocellular Carcinoma Patients*

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# دور ميثلة البادئ الضال في مرضي الالتهاب الكبدي المزمن و سرطان الكبد

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# ABSTRACT

Hepatocellular carcinoma (HCC) is one of the few tumors in which the incidence is on the rise worldwide. The increasing incidence of HCC is associated with the rise in hepatitis C virus (HCV) infection. Egypt has the highest prevalence of HCV/genotype 4 infection in the world, with 14% of the population infected. Little is known about the role(s) of epigenetic changes that may participate in HCV-induced HCC. Epigenetic studies directed at mapping the etiology of HCV disease progression to HCC and how they correlate with patients clinicopathological parameters are expected to provide new insights that will aid in the design of effective strategies for earlier detection and management of the disease. The aim of the current study was to investigate the aberrant methylation of 11 genes in liver tissue samples obtained from Egyptian patients infected with HCV/genotype 4, and to explore possible relationships between aberrant methylation and clinicopathological features in HCC. Thirty-one HCC and matching non-tumor tissues, thirty-four chronic hepatitis liver tissues, and thirteen normal liver tissues were analyzed for the methylation status of APC, FHIT, p15, p73, p14, p16, DAPK1, CDH1, RARβ, RASSF1A and $O^6$MGMT genes by qualitative methylation-specific PCR. Based on methylation profiles, a methylation of only 7 genes was found to be highly significant, which is dependent on disease state. Our data indicate that DNA methylation may serve as a marker for HCV-associated HCC, and demonstrate the importance of considering the clinicopathological variables as predicators of disease state.

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# ABBREVIATIONS

| | |
|---|---|
| **AAIR** | Age-adjusted Incidence Rate |
| **5- aza-cdR** | 5- aza- deoxycytidine |
| **AASLD** | American Association for the Study of Liver Disease |
| **AFP** | Alpha-fetoprotein |
| **AFP-L3** | Lectin-bound Alpha fetoprotein |
| **AML** | Acute Myelogenous Leukaemia |
| **APC** | Adenomatosis Polyposis Coli |
| **ARF** | Alternative Reading Frame |
| **CAH** | Chronic Active Hepatitis |
| **CDH** | E-Cadherin |
| **CDKN2a** | Cyclin- Dependent Kinase INhibitor 2a |
| **CH** | Chronic Hepatitis |
| **CLL** | Chronic Lymphocytic Leukaemia |
| **CML** | Chronic Myelogenous Leukaemia |
| **CpG** | Cytosine phosphate Guanine |
| **CRP** | Chromatin Remodeling Protein |
| **CT** | Computed Tomography Scan |
| **DAPK** | Death-Associated Protein Kinase |
| **DHF** | Dihydrofolate |
| **DN** | Dysplastic Nodules |
| **DNMT** | DNA methyltransferase |
| **ECM** | Extra Cellular Matrix Components |
| **ER** | Endoplasmic Reticulum |
| **FAP** | Family Adenomatous Polyposis |
| **FHIT** | Fragile Histidine Triad |
| **HATs** | Histone Acetyltransferases |
| **HDACs** | Histone Deacetylases |
| **HMTs** | Histone Methyltransferases |
| **HP** | Heterochromatin Protein |
| **HVR** | Hypervariable region |
| **IDU** | Injection Drug use |
| **IFN_α** | Interferon-α |
| **INK4a** | INhibitor of Cyclin dependent kinase 4a |

| | |
|---|---|
| **MBD** | Methyl CpG binding Domain |
| **MDM2** | Murine Double Minute 2 |
| **MeCP** | Methyl CpG binding Protein |
| **MGMT** | Methyl guanine DNA- Methyltransferase |
| **miRNAs** | Micro ribonucleic Acids |
| **MRI** | Magnetic Resonance Imaging |
| **MS** | Methionine Synthase |
| **MS-PCR** | Methylation specific Polymerase Chain Reaction |
| **MTHFR** | Methylene Tetrahydrofolate reductase |
| **MTs-1** | Major Tumor suppressor-1 |
| **NAFLD** | Non-Alcoholic Fatty Liver Disease |
| **NASH** | Non-alcoholic Steatohepatitis |
| **NS** | Non-Structural |
| **NSCLC** | Non-Small Cell Lung Cancer |
| **NTR** | Non-Translated Region |
| **ORF** | Open Reading Frame |
| **RARβ** | Retinoic Acid Receptor beta |
| **RASSF1A** | RAS association domain Family1 isoform A |
| **RT-PCR** | Real Time Polymerase Chain Reaction |
| **SAH** | *S*- adenosylhomocysteine |
| **SAM** | *S*- adenosylmethionine |
| **TAE** | *Tris* Acetate EDTA |
| **TDG** | Thymine DNA Glycosylase |
| **THF** | Tetrahydrofolate |
| **TMB** | Tetramethyl benzidine |
| **TSGs** | Tumor Suppressor Genes |
| **UDG** | Uracil DNA Glycosylase |
| **UMP** | Uridine monophosphate |

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