



The Detection of PNPLA3 Gene in Non Alcoholic Fatty Liver Disease Among Egyptian Patients

Thesis

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Internal Medicine

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Abstract

Introduction: Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver diseases with key stages consisting of hepatic steatosis , steatohepatitis (NASH), fibrosis, and eventual cirrhosis. NAFLD affects more than 20% of population worldwide. Imaging studies and laboratory tests do not reliably differentiate patients with NAFLD from those with NASH, or predict the severity of liver disease.

Aims: To estimate the prevalence of PNPLA3 gene in Egyptian patient with NAFLD and its relation to degree of hepatic affection.

Methodology: This study was conducted on 80 subjects they were subjected to full history taking and thorough physical examination, full anthropometric measurements, laboratory studies. The study was conducted at the gastroenterology and hepatology outpatient clinic of Helwan University Hospital (Badr Hospital) and Ain shams University Hospital.

Results: The patients were divided into 3 subgroups: Group 1 included patients with *simple steatosis*, Group 2 included patients with *NASH* and Group 3 included 10 age-matched healthy subjects as a *control* . PNPLA3 gene was detected in all groups

Concluded: There is an association between PNPLA3 gene with the incidence of NAFLD and progression to NASH in the Egyptian patients.

Recommendations: This study must be done in a wide scale of patients to estimate the prevalence of PNPLA3 gene in the Egyptian patients.

PNPLA3 can be added to the diagnostic panel and scoring systems in NAFLD to differentiate simple steatosis from NASH

Keywords: Detection of PNPLA3 Gene, Non Alcoholic, Fatty Liver Disease, Egyptian Patients

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

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List of Abbreviations

AAR: AST/ALT ratio.

AASLD: American Association for the Study of Liver Diseases.

ABHD5: α/β hydrolase domain containing-5.

ACO: Acetyl CO-A.

ADP: Adenosine Diphosphate.

ADPN: adiponutrin

AFLD: Alcoholic Fatty Liver Disease.

ALP: Alkaline Phosphatase.

ALT: Alanine Aminotransferase.

AMPK: AMP-Activated Kinase.

ANGPTL3: Angiopoietin-like Protein 3.

AP-1: Activator protein 1.

Apo B: Apolipoprotein B.

ApoB100: Apolipoprotein B100.

APOC3: Apo lipoprotein C3 gene

APPL1: Adaptor Protein containing Pleckstrin homology domain.

APRI: Aspartate Aminotransferase to Platelet Ratio Index.

ARBs: Angiotensin II receptor blockers

List of Abbreviations

ARFI: Acoustic Radiation Force Impulse.

ASH: Alcoholic Steatohepatitis.

AST: Aspartate aminotransferase.

ATGL: adipose triglyceride lipase.

ATP: Adenosine Triphosphate.

BAT: Brown adipose tissue.

BMI: Body Mass Index.

BMSC: bone marrow stromal cell.

CAP: Controlled Attenuation Parameter.

CAR: Constitutive Androstane Receptor.

CCl₄: Carbon tetrachloride.

CGI-58: Comparative gene identification-58.

cGMP: Cyclic Guanidine Monophosphate.

CK-18: CytoKeratin-18.

CLD: Chronic Liver Disease..

CREBP: Carbohydrate Response Element Binding Protein.

CRP: C-Reactive Protein.

CRN: Clinical Research Network

CT: Computed Tomography.

DM2: Type 2 diabetes mellitus

List of Abbreviations

DNA: Deoxy Ribonucleic Acid.

DPI: Doppler Perfusion Index.

ECs: Endothelial Cells.

ELF: Enhanced Liver Fibrosis.

ELISA: Enzyme Linked Immuno-Sorbent Assay.

eNOS: Endothelial Nitric Oxide Synthase.

EOS: Ethanol Oxidizing System.

EPA: Eicosapentaenoic Acid.

ER: Endoplasmic Reticulum.

FA: Fatty acid.

FBS: Fasting Blood Sugar.

FFA: Free Fatty Acids.

FLI: Fatty Liver Index.

G6pase: Glucose-6-phosphatase.

Gck: Glucokinase.

GGT: Gamma Glutamyl Transferase.

GLP-1: Glucagon-Like Peptide-1

GLUT-4: Glucose transporter – 4.

GWA: Genome-wide association

GS2: Gene sequence-2.

List of Abbreviations

- HA:** Hyaluronic Acid.
- HAART:** Highly Active Antiretroviral Drugs.
- HBsAg:** Hepatitis B Surface Antigen.
- HCC:** hepatocellular carcinoma
- HCVAb:** Hepatitis C Virus Antibody.
- HDL:** High Density Lipoprotein .
- HFE:** Hemochromatosis gene mutation.
- HIV:** Human Immunodeficiency Virus.
- HMW:** High Molecular Weight.
- HOMA:** Homeostasis Model Assessment.
- HSCs:** Hepatic Stellate Cells.
- HSL:** Hormone-sensitive lipase.
- HU:** Hounsefield Unit.
- I148M:** isoleucine 148 methionine.
- ICAM:** Intercellular Adhesion Molecule.
- ICAM-1:** Intercellular Adhesion Molecule-1
- IDF :** International Diabetes Federation (IDF)
- IFN:** Interferon.
- IL:** Interleukin.
- IL-6:** Interleukin-6.

List of Abbreviations

INAD: infantile neuroaxonal dystrophy.

iPLA₂: calcium-independent phospholipase A₂.

IR: Insulin Resistance.

IRF: IFN Regulatory Factor.

IU: International Unit.

IV: Intra Venous.

KC: Kupffer cells

KDa: KiloDalton.

Kg: Kilogram.

LCAT: Lecithin Cholesterol Acetyl Transferas.

LDL: Low Density Lipoprotein.

LPC: lysophosphatidylcholine.

LPS: LipoPolySaccharides.

LT: Lymphotoxin.

LTX: Liver transplantation

MAPK: Mitogen Activated Protein Kinase.

MAPKAP: MAPK activate protein kinase.

MKKK: MAPK kinase kinase.

MCP-1: Monocyte Chemoattractant Protein-1.

MiRNA: Micro RNA.

List of Abbreviations

mL: Milliliter.

mg: Milligram

Mm: Millimeter.

MPO: Myeloperoxidase.

MRC: Mitochondrial Respiratory Chain.

MRI: Magnetic Resonance Imaging.

mRNA: Messenger Ribonucleic Acid.

MRS: Magnetic Resonance Spectroscopy.

MS: Metabolic Syndrome.

MTP: Microsomal Triglyceride Transfer Protein

NAFLD: Non Alcoholic Fatty Liver Disease.

NAFL: Non Alcoholic Fatty Liver

NAS: NAFLD Activity Score.

NASH CRN: Nonalcoholic Steatohepatitis Clinical Research Network.

NASH: Non Alcoholic Steatohepatitis.

NASHES: National Health and Nutritional Evaluation Survey.

NBIA: neurodegeneration with brain iron accumulation.

NCEP ATP-III: National Cholesterol Education Program:
Adult Treatment Program I.

NEFA: Non-Esterified Fatty Acids.

List of Abbreviations

NF- κ B: Nuclear Factor Kabba.

NFS: NAFLD Fibrosis Score.

NNFL: Non-NASH Fatty Liver.

NO: Nitric Oxide.

NPV: Negative Predictive Value.

NRE: neuropathy target esterase-related esterase.

NT: Nash Test.

NTE: Neuropathy target esterase.

OELF: Original European Liver Fibrosis.

OSA: Obstructive Sleep Apnea.

P3NP: Procollagen III N-peptide.

PC: Phosphatidylcholine.

PCR: Polymerase Chain Reaction.

PIO: Pioglitazone

PDGF: Platelet Derived Growth Factor.

PEPCK1: Phospho Enol Pyruvate Carboxy Kinase 1.

PLA: phospholipase A.

PLA2G6: phospholipase A₂ group VI.

PNPLA: patatin-like phospholipase.

PPARs: Peroxisomal Proliferator Activated Receptors.

List of Abbreviations

PPV: Positive Predictive Value.

PTX: Pentoxypheiline

Pro: Proline.

PSC: Primary sclerosing cholangitis.

PTX 3: Plasma Pentraxin 3.

qPCR: Quantitative Real Time PCR.

RAS: Renin angiotensin system

RCT: Randomized controlled trial

RE: Retinol ester.

REC: Research Ethical Committee.

RES: Reticuloendothelial system.

RFLP: Restriction Fragment Length polymorphism.

RNA: Ribonucleic Acid.

RNS: Reactive Nitrogen Species.

ROS: Reactive Oxygen Species.

RS: Reference SNP.

RSG: rosiglitazone

RT-PCR: Reverse Transcriptase- Polymerase Chain Reaction.

RXR: Retinoid X Receptor.

SD: Standard Deviation.

List of Abbreviations

SHP: Small Heterodimer Partner.

SNP: Single Nucleotide Polymorphism.

SPEA: Serum prolidase enzyme activity.

sRAGE: Soluble Receptor for Advanced Glycation End products.

SREBP: Sterol Regulatory Element Binding Protein.

ST: SteatoTest.

STAT: Signal Transducers and Activators of Transcription.

TACE: Tumor Necrosis Factor Alpha-converting Enzyme.

TAG: triacylglycerol.

TG: Triglycerides.

TIMP 1: Tissue-Inhibited matrix Metalloproteinase Inhibitor-1.

TNF: Tumor Necrosis Factor.

TPN: Total Parenteral Nutrition.

TRADD: TNF receptor associated Death domain protein.

TRAF: TNF receptor associated factor.

TZD: Thiazolidinediones.

U/L: Unit/Liter.

UCP2: Uncoupling protein 2.

UDCA: Ursodeoxycholic Acid.

List of Abbreviations

ULN: Upper Limit of Normal.

US: UltraSonography.

USA: United States of America.

VCTE: Vibration Control Transient Elastography.

VLDL: Very Low Density Lipoproteins.

VSMCs: Vascular Smooth Muscle Cells.

WC: Waist circumference

WAT: White adipose tissue.

μM: Micro Meter.