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Review Article

Fat in the Liver - Is It All Happening in the Genes?

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Abstract

Fatty liver is a chronic liver disease characterized by excessive accumulation of fat, especially triglycerides, in the liver effecting both hemispheres of the globe equally. It is a non-communicable pandemic, which is on the rise and is held responsible for adding huge burden of chronic hepatitis, liver cirrhosis and even hepatocellular carcinoma. Contrary to our initial belief that fatty liver is a life-style disease, it is increasingly recognized that onset and progression of chronic hepatitis and fibrosis in fatty liver is due to an interplay genetic and environmental factors. In this review, we shed light on some of the genes that have been implicated for fatty liver.

Keywords: Fatty Liver; Gene; Steatohepatitis; Hepatic Fibrosis

Introduction

Fatty liver is characterized by excess accumulation of triglycerides (TG) in the liver [1,2]. It is a global pandemic and in the United States this particular liver condition is now the second leading indication for liver transplantation [3]. Fatty liver has varied spectrum on presentations. On one extreme, this condition can be benign, self-limiting, but on the other extreme can lead to

chronic hepatitis, liver cirrhosis and even hepatocellular carcinoma (HCC) [2,4]. Fatty liver related chronic hepatitis can be seen in upto 20% individuals harboring excess fat in their livers [5]. The overall prevalence of fatty liver varies from 15-40% and 9-40% in the West and in Asia respectively [6,7]. It has been estimated that approximately 25% of the population of the world has fatty liver [8].

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The prevalence of fatty liver and it's progression to steatohepatitis can not be explained by environmental factors only. Familial and twin studies strongly suggest that fatty liver may be a hereditary disease [9,10]. Monozygotic twins have more steatosis and fibrosis compared to dizygotic twins. First degree relatives of fatty liver patients also have higher risk of accumulating excess fat in the liver compared to the general population [9,11].

The onset of steatohepatitis in fatty liver is considered to be due to an interplay genetic and environmental factors, where oxidative stress plays major role [12]. It has been suggested that single nucleotide polymorphisms (SNPs) in genes involved in oxidative stress influence progression of steatosis to steatohepatitis [13].

Variants of several genes have been implicated for fatty liver including, patatin-like phospholipase domain-containing 3, transmembrane 6 superfamily 2, glutathione S-transferases genes, glucokinase regulator, gene encoding catalase and membrane bound O-acyltransferase domain containing 7.

Patatin-like phospholipase domain-containing 3 (PNPLA3)

PNPLA3 plays crucial role in lipid regulation of hepatocytes and stellate cells. It catalyzes the transfer of polyunsaturated fatty acids from di- and triacylglycerols to phosphocholines [14]. Genomewide association study (GWAS) identified PNPLA3 I148M variant as predominant genetic risk factor for the accumulation of fat in the liver [15,16]. It was first revealed in 2008 and after 2019, numerous GWAS have established PNPLA3 I148M variant as a genetic modifier for steatohepatitis, hepatic fibrosis and HCC [17]. A meta-analysis involving more than 14000 fatty liver patients reveals that M-variants (CG and GC) were associated with 3.24 and 2.14-folds higher odds of HCC than those homozygous for wild type (CC) [18]. PNPLA3 M-variants are associated with higher risk of decompensation of LC, HCC and liver-related deaths among biopsyproven fatty liver patients [19].

PNPLA3 is associated with response to life-style interventions too. Individuals who have I148M mutations are more responsive to carbohydrate and calory restriction [8]. It has also been shown that those who have PNPLA3 148I/M variant benefit more from hepatic steatosis, steatohepatitis and fibrosis following use of statins [20].

Transmembrane 6 superfamily 2 (TM6SF2)

Point mutation in TM6SF2 gene (rs58542926, c.499 C>T. P. Glu167Lys, E167K) has been identified to be independently associated with excess TG in the liver as well es elevation of serum alanine aminotransferase (ALT) [21-23]. Larger multiethnic cohort studies have also confirmed the association between TM6SF2 E167K and fatty liver [24-28]. In fact, a study involving more than 1200 Europeans revealed positive association between TM6SF2 E167K variant and steatohepatitis and hepatic fibrosis [29]. TM6SF2 E167K variant is also associated with excess liver fat in children and adolescents [30,31]. Individuals who have lean fatty liver usually carry TM6SF2 rs58542926 (T) allele more than those who are obese having fatty liver [32].

Glutathione S-transferases genes (GSTs)

GSTs are important in anti-oxidant defense and acts by inactivating products of oxidative stress [33]. They are enzymes in the second-stage detoxification system that catalyze reduced glutathione sulfhydryl groups, neutralize lipid and DNA oxidation products and exert protective effects against endogenous oxidative stress and exogenous toxins [34,35]. GWAS verifies crucial role of GSTs in onset and progression of fatty liver [36]. A recent meta-analysis suggested significant correlation between GSTM1, GSTT1 and GSTP1 genes SNPs and fatty liver vulnerability [36]. In addition to fatty liver, GSTs have also been associated with parkinsonism, asthma and several malignancies [36]. A recent study in an Asian cohort demonstrated that the risk for development of fatty liver increased significantly in presence of GSTM1-null genotype and combined distribution of GSTM1-null and GSTT1-null genotypes (Figure 1 and 2) [37].

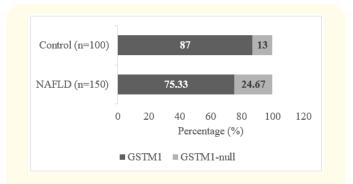


Figure 1: Frequency distribution of GSTM1 and GSTM1-null among fatty liver (NAFLD) patients and healthy controls.

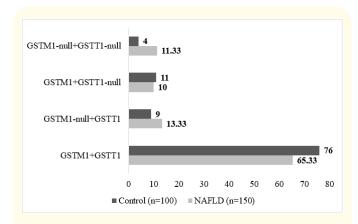


Figure 2: Frequency distribution of combinations of GSTM1 and GSTT1 genotypes in fatty liver (NAFLD) patients and healthy controls.

Glucokinase regulator (GCKR)

GCKR controls glucose influx into hepatocytes and regulates denovo lipogenesis [38]. The missence variant rs780094 of GCKR is associated with 1.2 fold higher risk of developing fatty liver [39]. Significant association between GCKR variant rs780094 and fatty liver has also been established in Indian and Chinese population [38,40].

Gene encoding catalase

Catalese is highly expressed in liver and since genetic polymorphism results in abnormal protein synthesis, this may lead to excess fat in the liver. It has been suggested that the important genetic variants of SOD2, CAT and GPX1 is associated with development of steatohepatitis [41].

A recent study, however, failed to demonstrate any significant difference in the frequency of CT and TT genotypes between fatty liver patients and healthy individuals in an Asian cohort (Figure 3 and 4) [42].

Membrane bound 0-acyltransferase domain containing 7 (MBOAT7)

MBOAT7 encodes for lysophospholipid acyltransferase-1 enzyme, which remodels membranes. It catalyzes desaturation of of the second acyl-chain of phospholipids and transfers

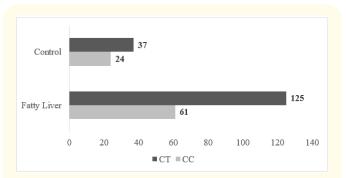


Figure 3: Frequency distribution of CC and CT genotypes in fatty liver patients and healthy controls.

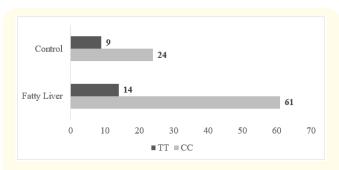


Figure 4: Frequency distribution of CC and TT genotypes in fatty liver patients and healthy controls.

polyunsaturated fatty acid to lysophosphatidylinositol and other phospholipids. It is fine regulator of arachidonic acid. Loss of arachidonic acid function triggers hepatic inflammation and fibrosis [43].

Super oxide dismutase 2 (SOD2)

SOD2 is one of the key enzymatic antioxidant defense mechanisms in cells [44]. It catalyzes dismutation of superoxide radicals to hydrozen peroxide ($\rm H_2O_2$) and oxygen in mitochondria constituting the first-line defense against reactive oxygen species (ROS) in mitochondria. 47 T>C (rs4880) genetic variation of SOD2 is significantly associated with of increased risk of fatty liver induced chronic hepatitis [41]. A recent study in an Asian cohort, however failed to revealed any positive correlation between this mutation and fatty liver (Figure 5).

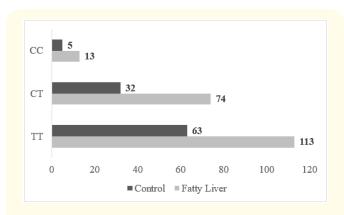


Figure 5: Frequency of distribution of CC, CT and TT genotype among fatty liver patients and control group [45].

Conclusion

The mainstay of fatty liver management as of date is life-style modification. Although a couple of drugs have recently been approved as pharmacotherapy for fatty liver, we still have to go a long way before we can confidently say that the progression of fatty liver can be halted. Understanding and unveiling the genetic basis of fatty liver remains crucial this will pave the way preventive and therapeutic interventions for fatty liver. Besides this will allow clinicians to identify those who are at increased risk of disease progression, even in the absence of histologic evidence of steatohepatitis, and manage them accordingly. Besides, this will also pave the way for development of drugs that will target the biological pathways affected by genetic variants which lead to fatty liver. Incorporation of fatty liver genetic modifiers into future clinical risk prediction tools and treatment algorithms appears to be inevitable.

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