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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 being recognized that onset and progression of chronic hepatitis and fibrosis in fatty liver is due to an interplay between 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 of presentations. On one extreme, this condition can be benign, self-limiting, but on the other extreme it 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 have fatty liver [8].

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 between 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]. Genome-wide 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 biopsy-proven 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 multi-ethnic 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

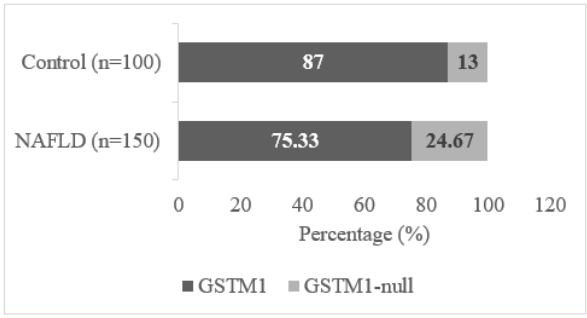

Figure 1: Frequency distribution of GSTM1 and GSTM1-null among fatty liver (NAFLD) patients and healthy controls.

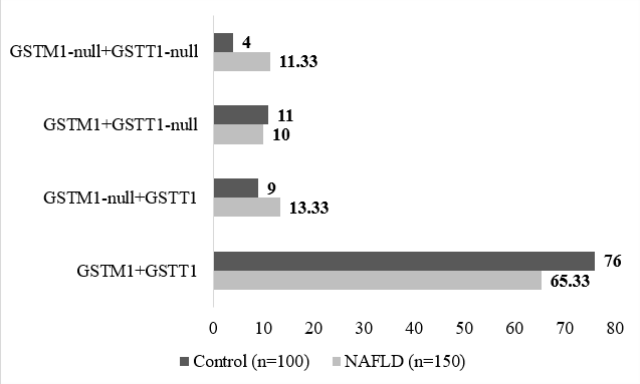

Figure 2: Frequency distribution of combinations of GSTM1 and GSTT1 genotypes in fatty liver (NAFLD) patients and healthy controls.

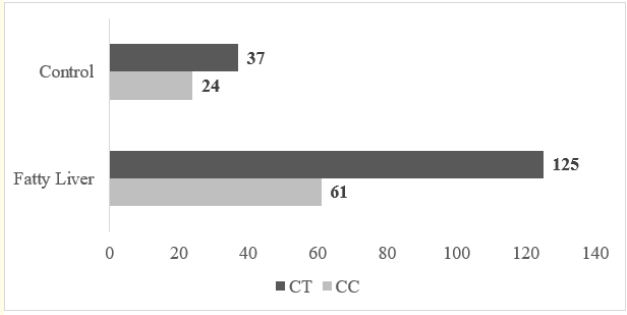

Figure 3: Frequency distribution of CC and CT genotypes in fatty liver patients and healthy controls.

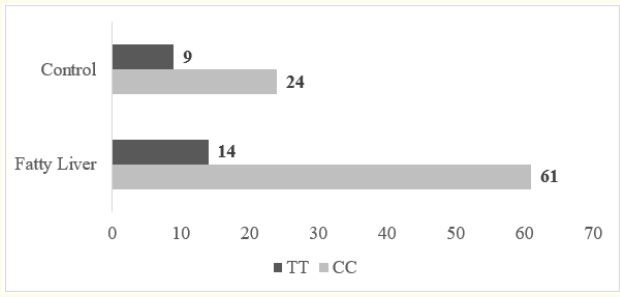

Figure 4: Frequency distribution of CC and TT genotypes in fatty liver patients and healthy controls.

combined distribution of GSTM1-null and GSTT1-null genotypes (Figure 1 and 2) [37].

Glucokinase regulator (GCKR)

GCKR controls glucose influx into hepatocytes and regulates de-novo 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 populations [38,40].

Gene encoding catalase

Catalese is highly expressed in liver and since genetic polymorphism results in abnormal fat 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 O-acyltransferase domain containing 7 (MBOAT7)

MBOAT7 encodes for lysophospholipid acyltransferase-1 enzyme, which remodels membranes. It catalyzes desaturation of the second acyl-chain of phospholipids and transfers 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 (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 reveal any positive correlation between this mutation and fatty liver (Figure 5).

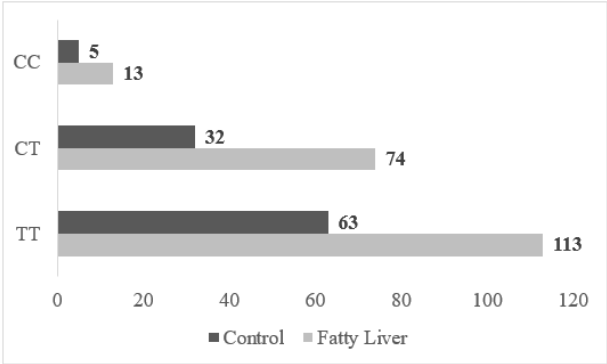

Figure 5: Frequency of distribution of CC, CT and TT genotype among fatty liver patients and control group [45].

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 as this will pave the way for 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.

Bibliography

1. Cohen JC., *et al*. "Human fatty liver disease: old questions and new insights". *Science* 332.6037 (2011): 1519-1523.

2. Friedman SL., *et al*. "Mechanisms of NAFLD development and therapeutic strategies". *Nature Medicine* 24.7 (2018): 908-922.

3. Wong RJ., *et al*. "Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States". *Gastroenterology* 148.3 (2015): 547-555.

4. Hobbs HH. "Science, serendipity, and the single degree". *Journal of Clinical Investigation* 128.10 (2018): 4218-4223.

5. Argo CK and Caldwell SH. "Epidemiology and natural history of non-alcoholic steatohepatitis". *Clinical Liver Disease* 13.4 (2009): 511-531.

6. Farrell GC and Larter CZ. "Nonalcoholic fatty liver disease: from steatosis to cirrhosis". *Hepatology* 43.2 (2006): S99-S112.

7. Lazo M and Clark JM. "The epidemiology of nonalcoholic fatty liver disease: a global perspective". *Seminar on Liver Disease* 28.4 (2008): 339-350.

8. Yuan L and Terrrault NA. "PNPLA3 and nonalcoholic fatty liver disease: towards personalized medicine for fatty liver". *Hepatobiliary Surgery Nutrition* 9.3 (2020): 353-356.

9. Willner IR., *et al*. "Ninety patients with nonalcoholic steatohepatitis: insulin resistance, familial tendency, and severity of disease". *American Journal of Gastroenterology* 96.10 (2001): 2957-2961.

10. Struben VM., *et al*. "Nonalcoholic steatohepatitis and cryptogenic cirrhosis within kindreds". *American Journal of Medicine* 108.1 (2000): 9-13.

11. Schwimmer JB., *et al*. "Heritability of nonalcoholic fatty liver disease". *Gastroenterology* 136.5 (2009): 1585-1592.

12. Kolesnikova OV., *et al*. "Influence of Resistance on Cardiometabolic Risk in Non-Alcoholic Fatty Liver Disease Patients Combined with Subclinical Hypothyroidism". *Metabolism - Clinical and Experimental* 116.154587 (2021).

13. Hardwick RN., *et al*. "Altered UDP-glucuronosyltransferase and sulfotransferase expression and function during progressive stages of human nonalcoholic fatty liver disease". *Drug Metabolism and Disposition* 41.3 (2013): 554-561.

14. Luukkonen PK., *et al*. "Human PNPLA3-I148M variant increases hepatic retention of polyunsaturated fatty acids". *JCI Insight* 4.16 (2019): e127902.

15. Romeo S., *et al*. "Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease". *Nature Genetics* 40.12 (2008): 1461-1465.

16. Yuan X., *et al*. "Population-based genome-wide association studies reveal six loci influencing plasma levels of liver enzymes". *American Journal of Human Genetics* 83.4 (2008): 520-528.

17. Anstee QM and Day CP. "The Genetics of Nonalcoholic Fatty Liver Disease: Spotlight on PNPLA3 and TM6SF2". *Seminar on Liver Disease* 35.3 (2015): 270-290.

18. Dai G., *et al*. "Association between PNPLA3 rs738409 polymorphism and nonalcoholic fatty liver disease (NAFLD) susceptibility and severity: A meta-analysis". *Medicine (Baltimore)* 98.7 (2019): e14324.

19. Grimaudo S., *et al*. "Association Between PNPLA3 rs738409 C>G Variant and Liver-Related Outcomes in Patients With Nonalcoholic Fatty Liver Disease". *Clinical Gastroenterology and Hepatology* 18.4 (2020): 935-944.e3.

20. Dongiovanni., *et al*. "Statin use and non-alcoholic steatohepatitis in at risk individuals". *Journal of Hepatology* 63.3 (2015): 705-712.

21. Kozlitina J., *et al*. "Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease". *Nature Genetics* 46.4 (2014): 352-356.

22. Holmen OL., *et al*. "Systematic evaluation of coding variation identifies a candidate causal variant in TM6SF2 influencing total cholesterol and myocardial infarction risk". *Nature Genetics* 46.4 (2004): 345-351.

23. Mahdessian H., *et al*. "TM6SF2 is a regulator of liver fat metabolism influencing triglyceride secretion and hepatic lipid droplet content*". Proceedings of the National Academy of Sciences of the United States of America* 111.24 (2014): 8913-8918.

24. Liu DJ., *et al*. "Exome-wide association study of plasma lipids in >300,000 individuals". *Nature Genetics* 49.12 (2017): 1758-1766.

25. Anstee QM., *et al*. "Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterised cohort". *Journal of Hepatology* 73.3 (2020): 505-515.

26. Parisinos CA., *et al*. "Genome-wide and Mendelian randomisation studies of liver MRI yield insights into the pathogenesis of steatohepatitis". *Journal of Hepatology* 73.2 (2020): 241-251.

27. Chen VL., *et al*. "Genetic variants that associate with cirrhosis have pleiotropic effects on human traits". *Liver International* 40.2 (2024): 405-415.

28. Zhou Y., *et al*. "Circulating triacylglycerol signatures and insulin sensitivity in NAFLD associated with the E167K variant in TM6SF2". *Journal of Hepatology* 62.3 (2015): 657-663.

29. Liu YL., *et al*. "TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease". *Nature Communication* 5 (2014): 4309.

30. Mancina RM., *et al*. "Transmembrane-6 superfamily member 2 (TM6SF2) E167K variant increases susceptibility to hepatic steatosis in obese children". *Digestive and Liver Disease* 48.1 (2016): 100-101.

31. Grandone A., *et al*. "TM6SF2 Glu167Lys polymorphism is associated with low levels of LDL-cholesterol and increased liver injury in obese children". *Pediatric Obesity* 11.2 (2016): 115-119.

32. Chen F., *et al*. "Lean NAFLD: A Distinct Entity Shaped by Differential Metabolic Adaptation". *Hepatology* 71.4 (2020): 1213-1227.

33. Bolt HM and Thier R. "Relevance of the deletion polymorphisms of the glutathione S-transferases GSTT1 and GSTM1 in pharmacology and toxicology". *Current Drug Metabolism* 7.6 (2006): 613-628.

34. Khan AJ., *et al*. "Polymorphism in glutathione-S-transferases: a risk factor in alcoholic liver cirrhosis". *Drug and Alcohol Dependence* 101.3 (2009): 183-190.

35. Kassogue Y., *et al*. "Association of glutathione S-transferase (GSTM1 and GSTT1) genes with chronic myeloid leukemia". *Springerplus* 4 (2015): 210.

36. Zhu Y., *et al*. "Association of glutathione S-transferases (GSTT1, GSTM1 and GSTP1) genes polymorphisms with nonalcoholic fatty liver disease susceptibility: A PRISMA-compliant systematic review and meta-analysis". *Medicine (Baltimore)* 101.38 (2022): e30803.

37. Arafin SM. "Association of Glutathione S Transferase M1 and T1 genotype (genetic polymorphism) with non-alcoholic fatty liver disease". Thesis submitted to Bangladesh Medical University for partial fulfillment of Doctor of Medicine in Hepatology (2023).

38. Chavan SU., *et al*. "Association of GCKR and MBOAT7 genetic polymorphisms with non-alcoholic fatty liver disease". *Clinical and Experimental Hepatology* 10.1 (2024): 39-46.

39. Zain SM., *et al*. "Common variant in the glucokinase regulatory gene rs780094 and risk of nonalcoholic fatty liver disease: a meta-analysis". *Journal of Gastroenterology and Hepatology* 30.1 (2015): 21-27.

40. Yang Z., *et al*. "Genetic variation in the GCKR gene is associated with non-alcoholic fatty liver disease in Chinese people". *Molecular Biology Reports* 38.2 (2012): 1145-1150.

41. Huang YS., *et al*. "Genetic variations of three important antioxidative enzymes SOD2, CAT, and GPX1 in nonalcoholic steatohepatitis". *Journal of the Chinese Medical Association* 84.1 (2021): 14-18.

42. Mazmadar KAH. "Association of genetic polymorphism of gene encoding catalase with non-alcoholic fatty liver disease". Thesis submitted to Bangladesh Medical University for partial fulfillment of Doctor of Medicine in Hepatology (2024).

43. Zarini S., *et al*. "Lysophospholipid acyltransferases and eicosanoid biosynthesis in zebrafish myeloid cells". *Prostaglandins & Other Lipid Mediators* (2014): 113-115:52-61.

44. Gonzalez-Pinto A., *et al*. "Antioxidant defense system and family environment in adolescents with family history of psychosis". *BMC Psychiatry* 12 (2012): 200.

45. Masud FMMA. "Association of genetic polymorphism of gene encoding super oxide dismutase 2 enzyme with non-alcoholic fatty liver disease". Thesis submitted to Bangladesh Medical University for partial fulfillment of Doctor of Medicine in Hepatology (2023).