OPEN ACCESS Freely available online

Journal of Carcinogenesis &Mutagenesis

Review Article

Current Genetic Advances in NAFLD/NASH: Related Hepatocellular Carcinoma Along with Characteristic Clinical Manifestation

Kazumi Fujioka*

Department of Radiology, Nihon University School of Medicine, Tokyo, Japan

ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is the common liver disease worldwide because of the increasing rates in parallel to obesity and Type 2 Diabetes Mellitus (T2DM). Mechanically, lipid accumulation and insulin resistance serve as the first hit, second hit is considered as inflammation and fibrosis in NAFLD. NAFLD is attributed to liver-related morbidity and mortality, there is also growing evidence that NAFLD is a multisystem disease and is associated with hepatic (hepatocellular carcinoma: HCC) and extrahepatic (Cardiovascular Disease: CVD, Coronary Artery Disease: CAD, and Chronic Kidney Disease: CKD) diseases. The author previously suggested that an association between chronic liver disease (NAFLD/NASH and chronic hepatitis C virus infection: HCV infection) and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway. In this article, the current genetic advances of NAFLD/NASH-related HCC including PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13, and the combined effect of these variants along with characteristic clinical manifestation have been reviewed. NAFLDs clinically predispose to occur non-cirrhotic NAFLD-HCC. The study of polygenic risk scores may be attributed to the stratification of the risk of the NAFLD/NASH-related HCC in the near feature. On the basis of the characteristic clinical and genetic evidences, the author suggests that the risk stratification of the medium/high risk in NAFLD-related HCC, especially non-cirrhotic HCC may contribute to the prevention, prediction, and surveillance.

Keywords: NAFLD/NASH-related HCC; Non-cirrhosis NAFLD-HCC; Complex disease; Polygenic risk score; Atherosclerosis

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is the common liver disease worldwide due to the increasing rates in parallel to obesity and T2DM [1]. NAFLD is attributed to liver-related morbidity and mortality, there is also growing evidence that NAFLD is a multisystem disease and is associated hepatic (HCC) and extrahepatic (CVD, CAD, and CKD) diseases [2,3]. The author previously suggested that an association between chronic liver disease and atherosclerosis may be present due to the presence of the inflammation as a common pathway [4]. The clinical practice guidelines have suggested that NAFLD-related HCCs epidemiologically may develop in the pre-cirrhotic stage and genetically the PNPLA3 rs738409C> G gene polymorphism has been associated with an increased risk of HCC [3]. In this article, the author will review the current genetic advances of NAFLD/NASH-related HCC including PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13, and the combined effect of these variants along with characteristic clinical manifestation in detail.

LINK BETWEEN NAFLD/NASH AND ATHEROSCLEROSIS

The prevalence and incidence of NAFLD is increasing due to the epidemics of obesity and T2DM [1]. Many studies provided that NAFLD associates with endothelial dysfunction assessed by Flow-Mediated Vasodilation (FMD) study, increased Intima-Media Thickness (IMT) by evaluated common carotid artery, increased Pulse Wave Velocity (PWV), and increased coronary arterial calcifications that are established as CVD surrogate markers [2]. It has been indicated that NAFLD is part of a

Correspondence to: Kazumi Fujioka, Department of Radiology, Nihon University School of Medicine, Tokyo, Japan, Email: spbk2xq9@ninus.ocn.ne.jp

Received: March 08, 2021; **Accepted:** March 22, 2021; **Published:** March 29, 2021

Citation: Fujioka K (2021) Current Genetic Advances in NAFLD/NASH: Related Hepatocellular Carcinoma Along with Characteristic Clinical Manifestation. J Carcinog Mutagen. S17:001.

complex multisystem disease with multiple bidirectional relationships [2]. The clinical practice guidelines suggested that the consensus is that CVD should be identified in NAFLD irrelevant of the presence of traditional or classical risk factors [3]. The author previously described that an association between chronic liver disease and systemic atherosclerosis may be present due to the presence of the inflammation as a common pathway [4]. Endothelial dysfunction has been considered as an early surrogate marker in CVD and an initial step in atherosclerosis condition. Flow-Mediated Vasodilation (FMD) and Nitroglycerin-Mediated Vasodilation (NMD) tests in the brachial artery is a potential method for evaluating vascular endothelial and Vascular Smooth Muscle Cell (VSMC) function in atherosclerosis [5]. The author has described several studies on the diseases of migraine, CVD, Chronic Kidney Disease (CKD), dyslipidemia, aging liver, and COVID-19 [6-16] using FMD and NMD procedure.

CHARACTERISTIC CLINICAL MANIFESTATIONS IN NAFLD/NASH-RELATED HCC

Cirrhotic NAFLD-related HCC

The growing incidence has showed that NASH/NAFLD has led to an increase of NASH-related HCC [17]. Kanwal et al. described that the risk of HCC was higher in patients with NAFLD than that observed in general clinical population [18]. Most HCC occurs in patients with cirrhotic NAFLD. Grimaudo et al. described that all patients in their study had F3 fibrosis or cirrhosis status [19]. A meta-analysis indicated the severity of liver fibrosis as the main indicator of prognosis in NAFLD [20]

Non-cirrhotic NAFLD-related HCC

According to the clinical practice guidelines, studies have associated obesity and T2DM with the risk of HCC [3]. It also indicated that patients with NAFLD-associated HCC at diagnosis are older than those with non-NAFLD HCC, with a lower prevalence of cirrhosis [3]. A multicenter prospective study by HCC-NAFLD Italian Study Group indicated that NAFLD-related HCC is more often found at a later tumor stages and was more common than HCV-related HCC [21]. Gawrieh et al. noted that nearly 12% of HCCs developed in patient without cirrhosis from a United States multicenter study [22]. They described that NAFLD was the most common liver disease in these patients. The studies and a meta-analysis also described that non-cirrhotic HCC is more frequent in NASH compared with liver diseases derived from other etiologies [23]. Mohamad et al. mentioned that patients with non-cirrhotic NAFLD-related HCC are more likely to represent at an older age, larger tumor size, and higher rates of tumor recurrence [24]. It has been suggested that HCC development has been also identified in patients with non-cirrhotic NAFLD. Bengtsson et al. reported that patients with non-cirrhotic NAFLD-related HCC were observed in 37% of NAFLD-HCC [25]. The results provided that patients with non-cirrhotic NAFLD-HCC, compared with patients with cirrhotic NAFLD-HCC, were older, a lower prevalence of T2DM, larger tumors, and allocated treatments [25]. The report by Anstee et al. described that up to 49 % of NAFLD-related HCC develop in patients without cirrhosis [26].

The clinical practice guidelines suggested that NAFLD is a risk factor for HCC, which may develop in the pre-cirrhotic stage, and the risk is increased by the presence of the PNPLA3 rs738409 C>G polymorphism [3]. However, the guideline has not recommended HCC surveillance in patients with non-cirrhosis NAFLD [3]. While, Cholankeril et al. indicated that increased efforts of effective screening and preventative strategies especially in patient with non-cirrhotic NASH based on genetic susceptibility are needed to decrease the occurrence of NASH-related HCC [17].

CURRENT GENETIC ADVANCES IN NAFLD/NASH-RELATED HCC

PNPLA3

The clinical practice guidelines described that a higher liver fat content and increased risk of NASH were represented in carriers of the PNPLA3 I148M and the TM6SF2 E167K variants [3]. They recommended that genotyping may be regarded in selected patients and clinical studies [3]. Current studies indicated that genetic susceptibility increases risks of NAFLD, NASH, and NASH-related cirrhosis [27]. It has been previously reported that these five genes including PNPLA3, TM6SF2, GCKR, MBOAT7, and HSD17B13 known to be associated with NASH are involved in glucose and fat homeostasis regulatory pathways [27,28]. The most closely related genetic variant with NAFLD is PNPLA3-I148M, while variants in HSD17B13, MBOAT7, and GCKR have been recently implicated. It has been also suggested that PNPLA3-I 148M is modified by the interaction with other genetic polymorphism [29]. The study has provided the combined multiple genetic variants with other markers [29]. A nonsynonymous SNP in PNPLA3 known as rs 738409 c.444 C> G p.I148M is the first genetic variant found to be associated with NASH [27]. It is suggested that PNPLA3 I148M has allelic odds ratios of approximately two or three for risks of NAFLD, NASH, and HCC [19,27]. PNPLA3 I 148M has been associated with the fibrosis stage of NAFLD and HCC [30,31]. Liu et al. described that carriage of the PNPLA3 rs738409 C>G polymorphism is associated with greater risk of progressive steatohepatitis and fibrosis and HCC [31]. Grimaudo et al. suggested that patients with NAFLD carrying PNPLA3 rs738409 C>G variant are at higher risk of decompensation, liver cancer, and death [19]. Based on the studies, the author also emphasizes that genetically, the presence of the PNPLA3 rs738409C>G gene polymorphism has been associated with an increased risk of HCC. Recent report using GWAS of the NAFLD/NASH represented that PNPLA3-I 148M was confirmed to be associated with the full spectrum of disease [32]. Recently, Unalp-Arida et al. concluded that PNPLA3 I148M and higher NAFLD liver fat and fibrosis scores were associated with raised liver disease mortality in the U.S. population, indicating that genetic variant PNPLA3 I 148M may complement the liver disease indicators for surveillance in patients with NAFLD [33]. With respect to the childhood report, Tang et al. described that PNPLA3 gene polymorphism was significantly associated with susceptibility and severity of NAFLD from a meta-analysis study [34].

HSD17B13

It has been described that hydroxysteroid 17-beta dehydrogenase 13 (HSD17B13) act as a liver-specific, lipid droplet associated protein [29]. Ma et al. have found two causative variants including rs72613567 and rs62305723 in the HSD17B13 [35]. Abul-Husn et al. firstly have described the hepatoprotective effect of HSD17B13 rs72613567:TA [36]. The study has suggested the relation between variant in HSD17B13 and reduced risk of CLD and of progression [36]. These reports indicated that loss-of-function variants in HSD17B13 are protective for the occurrence of NASH and NAFLD cirrhosis [35, 36]. It has been studied that the association between the variant and reduced odds of HCC have been reported [37, 38]. Gellert-Kristensen et al. suggested that the ALT-lowering effect of the loss-of-function variant HSD17B13 rs72613567:TA is most pronounced among those at highest risk of fatty liver disease in the Danish general population [37].

TM6SF2

A SNP in TM6SF2 (transmembrane 6 superfamily member 2) is associated with increased liver fat content, NASH, advanced hepatic fibrosis and cirrhosis [39]. Exome-wide association studies demonstrated the rs58542926 C>T variant of the TM6SF2. The study indicated that the TM6SF2 E167K variant increases susceptibility to NASH and liver fibrosis, but are protected against CVD [39]. A meta-analysis represented the dual and opposite role of the TM6SF2-rs58542926 [40]. While, significantly relationship between a lower risk of NAFLD and CC genotype of TM6SF2 rs58542926 has been studied in the recent meta-analysis [41].

GCKR

A few studies indicated that a SNP in the glucokinase regulatory protein (GCKR) gene (rs780094) has been associated with NAFLD and fibrosis severity [42,43]. It has been reported that GCKR P446L is a loss-of-function variant and is associated with increased susceptibility to NAFLD, NASH, and NASH-related HCC [27,44]. The study also provided that risk evaluation using PRS showed the effect of the risk alleles [44].

MBOAT7

The study suggested that an association between membrane bound O-acyltransferase domain-containing 7 (MBOAT7) rs641738 genetic variant and development and severity of NAFLD was detected in individual of European descent [45]. While, it has been suggested that the MBOAT7 rs641738 T allele variant was associated with predisposition to HCC [46]. It has been also reported that a SNP downstream of the gene encoding MBOAT7 may predispose to HCC [47]. Anstee et al. recently described the GWAS of NAFLD/NASH in a histologically characterized cohort and concluded PNPLA3 as a risk factor for the full histological spectrum of NAFLD with potential contributions from TM6SF2 and HSD17B13 [32]. With respect to the NAFLD pathogenesis, they described PYGO1 as a novel steatosis modifier and indicated that Wnt signaling pathways may be relevant.

COMBINED EFFECT OF VARIANTS

The report by Gellert-Kristensen et al. suggested that a genetic risk score (GRS), combining the three genetic variants in PNPLA3 p.I148M, TM6SF2 p.E167K, and HSD17B13 rs72613567, was associated with cirrhosis and HCC in fatty liver including NAFLD and alcoholic type in individual from the general population [48]. They concluded a GRS showed risk of cirrhosis by up to 12-fold and risk of HCC by up to 29-fold. Martin et al. mentioned that risk prediction scores will be used in confirmed NAFLD for stratification of follow up, therapeutic, and surveillance [29].Meanwhile, the report indicated that the risk of occurrence of NAFLD and associated complications is determined by the environmental and genetic factors [4 9]. It has been also suggested that the development of polygenic risk scores have provided new impetus in NAFLD risk stratification [49].

RISK STRATIFICATION IN NAFLD/NASH-RELATED HCC

It has been known that NAFLD is a complex disease including HCC, CVD, CAD and other extrahepatic disease such as CKD [2,3]. Epidemiologically, many studies associated obesity and T2DM with the risk of HCC and NAFLD-associated HCC is a lower prevalence of cirrhosis. Whereas, the guidelines have recommended a closer monitoring in patient with cirrhotic NASH associated with hypertension. NAFLD-related HCCs may develop in the pre-cirrhotic stage and the PNPLA3 rs738409C>G gene polymorphism has been associated with an increased risk of HCC. Furthermore, the combined effect of common variants on risk of cirrhosis and HCC has also described. It is clinically known that NAFLDs predispose to occur non-cirrhotic NAFLD HCC. The author suggests that stratification of the medium and high risk of NAFLD related HCC based on the characteristic clinical and genetic studies especially non-cirrhotic HCC may contribute to the prevention, prediction, and surveillance.

THERAPEUTIC STRATEGY FOR NAFLD/NASH-RELATED HCC

Very limited evidence indicates that PNPLA3 I148M may modulate the response to therapy and HSD17B13 may provide targets for treatment strategy in patients with NASH [27]. While, Schwartz et al. revealed new signal pathways that regulate PNPLA3 transcription and conclude that momelotinib serve as a potential therapeutic benefit to a high-risk patients with NAFLD/NASH [50]. Whereas, Anstee et al. noted NAFLD-related HCC including the epidemiology such as adaptive and innate immune responses that promote hepatic carcinogenesis [26]. The immunological report showed that AKR1B10 and SPP1 are closely associated with three (B cells, DCs, and MAIT cells) in the progression of NAFLD. The study provided that TGX-221 may be an important treatment for the NAFLD and NAFLD-related HCC [51].

DISCUSSION

NAFLD is the common liver disease worldwide due to the increasing rates in parallel to obesity and T2DM. It is mechanically known that lipid accumulation and insulin resistance serve as the first hit, subsequently inflammation and

fibrosis play a role as a second hit. In this article, the current genetic advances of NAFLD/NASH-related HCC including PNPLA3, TM6SF2, GCKR, MBOAT7, HSD17B13, and combined effect of these variants along with characteristic clinical manifestation have been reviewed. Based on the characteristic clinical evidences, NAFLDs predispose to occur non-cirrhotic NAFLD-HCC. Genetically, the combining genetic studies may be attributed to the risk stratification in NAFLD/NASH-related HCC in the near feature. The author suggests that stratification of the medium/high risk of NAFLD-related HCC on the basis of the characteristic clinical and genetic evidences especially non-cirrhotic HCC may contribute to the prevention, prediction, and surveillance.

CONCLUSIONS

1. In addition to the epidemiological and single genetic factors, the study of combined effect of the variants may be attributed to the risk stratification in NAFLD/NASH-related HCC, because NAFLD is a complex disease and is associated with hepatic and extrahepatic manifestations.

2. The author suggests that the stratification of the risk of NAFLD-related HCC especially non-cirrhotic HCC based on the characteristic clinical and genetic evidences may contribute to the prevention, prediction, and surveillance.

CONFLICT OF INTEREST

Author declares that I have no conflicts of interest.

REFERENCES

1. Younossi ZM. Non-alcoholic fatty liver disease- a global public health perspective. J Hepatol. 2019;70(3):531-544.
2. Francque SM, Van der Graaff D, Kwanten WJ. Non-alcoholic fatty liver disease and cardiovascular risk: pathophysiological mechanisms and implications. J Hepatol 2016; 65(2):425-443.
3. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetelogia. 2016; 59(2): 1121-1140.
4. Fujioka K. Association between chronic liver disease and atherosclerosis: an inflammation as common pathway. J Clin Trials. 2021;11(1):444.
5. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39(2):257-265.
6. Fujioka K, Oishi M, Fujioka A, Nakayama T. Increased nitroglycerin-mediated vasodilation in migraineurs without aura in the interictal period. J Med Ultrason. 2018;45(5):605-610.
7. Fujioka K. Reply to: Endothelium-dependent and –independent functions in migraineurs. J Med Ultrason. 2019;46(8):169-170.
8. Fujioka K, Oishi M, Nakayama T, Fujioka A. Association of brachial artery measures with estimated GFR>60mL/min/1.73m^2 in a cross-sectional study of the community-based women. Angiol Open Access. 2019;7(2):231.
9. Fujioka K. Propensity to the vascular smooth muscle cell abnormality in migraine without aura and vasospastic angina along with a genome-wide association studies. J Carcinog Mutagene. 2019;10(2):334.
10. Fujioka K, Oishi M, Fujioka A, Nakayama T, Okada M. Interrelationship among lipid profiles, arterial stiffness, and nitroglycerin-mediated vasodilation in the community-based setting of Japanese women. Angiol Open Access. 2019; 7(3):235.
11. Fujioka K. Effect on microRNA-92a in atherosclerosis along with flow-mediated vasodilation study. J Cancer Oncol. 2020;4(1): 000153.
12. Fujioka K. A novel biomarker micro RNA-92a-3p as a link between cardiovascular disease and chronic kidney disease. J Carcinog Mutagen 2020;11 (2) 1000345.
13. Fujioka K, Oishi M, Nakayama T, Fujioka A. Correlation between vascular failure (endothelial dysfunction) and fibrosis markers. Jpn J Med Ultrsonics. 2016;43(4):S458.
14. Fujioka K. Association between endothelial dysfunction and aspartate aminotransferase to platelet ratio index in patient without hepatic-related disease. Angiol Open Access. 2021 (under review).
15. Fujioka K. NAFLD/NASH-related hepatocellular carcinoma: along with the role of genetics. J Cancer Oncol. 2020;4(2):000165.
16. Fujioka K. A link between endothelial dysfunction and SARS-CoV-2 infection in patients with COVID-19. CPQ Medicine 2021;11(4):1-8.
17. Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: current knowledge and implications for management. World J Hepatol. 2017;9(11):533-543.
18. Kanwal F, Kramer JR, Mapakshi S, Natarajan Y, Chayanupatkul M, Richardson PA, et al. Risk of hepatocellular cancer in patients with non-alcoholic fatty liver disease. Gastroenterol. 2018;155(6):1828-1837.
19. Grimaudo S, Pipitone RM, Pennisi G, Celsa C, Camma C, Marco VD, et al. Association between PNPLA3 rs738409 C>G variant and liver-related outcomes in patients with nonalcoholic fatty liver disease. Clin Gastronterol Hepatol. 2020;18(4):935-944.
20. Vilar-Gomez E, Calzadilla-Bertot L, Wai-Sun Wong V, Castellanos M, de la Fuente RA, Metwally M, et al. Fibrosis severity as a determinant of cause-specific mortality in patients with advanced nonalcoholic fatty liver disease: a multi-national cohort study. Gastroenterology. 2018;155(2):443-457. e17.
21. Piscaglia F, Svegliati-Baroni G, Barchetti A, Pecorelli A, Marinelli S, Tiribelli C, et al. Clinical patterns of hepatocellular carcinoma in nonalcoholic fatty liver disease: a multicenter prospective study. Hepatology. 2016;63(3):827-838.
22. Gawrieh S, Dakhoul L, Miller E, Scanga A, deLemos A, Kettler C, et al. Characteristics, aetiologies and trends of hepatocellular carcinoma in patients without cirrhosis: a United States multiicentre study. Aliment Pharmacol Ther. 2019;50(7):809-821.
23. Stine JG, Wentworth BJ, Zimmet A, Rinella ME, Loomba R, Caldwell SH, et al. Systematic review with meta-analysis: risk of hepatocellular carcinoma in non-alcoholic steatohepatitis without cirrhosis compared to other liver diseases. Aliment Pharmacol Ther. 2018;48(7):696-703.
24. Mohamad B, Shah V, Onyshchenko M, Elshamy M, Aucejo F, Lopez R, et al. Characterization of hepatocellular carcinoma (HCC) in non-alcoholic fatty liver disease (NAFLD) patients without cirrhosis. Hepatol Int 2016;10(4):632-639.
25. Bengtsson B, Stal P, Wahlin S, Bjorstrom N, Hagstrom H. Characteristics and outcome of hepatocellular carcinoma in patients with NAFLD without cirrhosis. Liver Int. 2019;39(6):1098-1108.
26. Anstee QM, Reeves HL, Kotsiliti E, Govaere O, Heikenwalder M. From NASH to HCC: current concepts and future challenges. Nat Rev Gastroenterol Hepatol. 2019;16(7):411-428.
27. Carlsson B, Linden D, Brolen G, LilJeblad M, Bjursell M, Romeo S, et al. Review article: the emerging role of genetics in precision medicine for patients with non-alcoholic steatohepatitis. Aliment Pharmacol Ther. 2020;51(12):1305-1320.
28. Valenti LVC, Baselli GA. Genetics of nonalcoholic fatty liver disease: a 2018 update. Curr Pharm Des. 2018; 24(38):4566-4573.

29. Martin K, Hatab A, Athwal VS, Jokl E, Hanley KP. Genetic contribution to non-alcoholic fatty liver disease and prognostic implications. Curr Diab Rep. 2021;21(3):8.
30. Rotman Y, Koh C,Zmuda JM, Kleiner DE, Liang TJ, NASH CRN. The association of genetic variability in patatin-like phospholipase domain-containing protein 3 (PNPLA3) with histological severity of nonalcoholic fatty liver disease. Hepatology. 2010;52(3):894-903.
31. Liu YL, Patman GL, Leathart JBS, Piguet AC, Burt AD, Dufour JF, et al. Carriage of the PNPLA3 rs738409 C>G polymorphism confers an increased risk of non-alcoholic fatty liver diseases associated hepatocellular carcinoma. J Hepatol. 2014;61(1):75-81.
32. Anstee QM, Darlay R, Cockell S, Meroni M, Govaere O, Tiniakos D, et al. Genome-wide association study of non-alcoholic fatty liver and steatohepatitis in a histologically characterized cohort. J Hepatol. 2020;73(3):505-515.
33. Unalp-Arida A, Ruhl CE. Patatin-like phospholipase domain-containing protein 3 I148M and liver fat and fibrosis scores predict liver disease mortality in the U. S. population. Hepatology. 2020;71(3):820-834.
34. Tang S, Zhang J, Mei TT, Guo HQ, Wei XH, Zhang WY, et al. Association of PNPLA3 rs738409 G/C gene polymorphism with nonalcoholic fatty liver disease in children: a meta-analysis. BMC Medical Genetics. 2020;21(4):163.
35. Ma Y, Belyaeva OV, Brown PM, Fujita K, Valles K, Karki S, et al. 17-beta hydroxysteroid dehydrogenase 13 is a hepatic retinol dehydrogenase associated with histological features of nonalcoholic fatty liver disease. Hepatology. 2019;69(4):1504-1519.
36. Abul-Husn NS, Cheng X, Li AH, Xin Y, Schurmann C, Stevis P, et al. A protein-truncating HSD17B13 variant and protection from chronic liver disease. N Engl J Med. 2018;378(12):1096-1106.
37. Gellert-Kristensen H, Nordestgaard BG, Tybjærg -Hansen A, Stender S. High risk of fatty liver disease amplifies the alanine transaminase-lowing effect of a HSD17B13 variant. Hepatology. 2020;71(1):56-66.
38. Yang J, Trepo E, Nahon P, Cao Q, Moreno C, Letouze E, et al. A 17-Beta- hydroxysteroid dehydrogenase 13 variant protects from hepatocellular carcinoma development in alcoholic liver disease. Hepatology. 2019; 70(1): 231-240.
39. Dongiovanni P, Petta S, Maglio G, Fracanzani AL, Pipitone R, Mozzi E, et al. Transmembrane 6 superfamily member 2 gene variant disentangles nonalcoholic steatohepatits from cardiovascular disease. Hepatology. 2015;61(2):506-514.
40. Pirola CJ, Sookoian S. The dual and opposite role of the TM6SF2-rs58542926 variant in protecting against cardiovascular disease and conferring risk for nonalcoholic fatty liver: a meta-analysis. Hepatology. 2015;62(6):1742-1756.
41. Xia Y, Huang CX, Li GY, Chen KH, Li H, Tang L, et al. Meta-analysis of the association between MBOAT7 rs641738, TM6SF2 rs58542926 and nonalcoholic fatty liver disease. Clin Res Hepatol Gastroenterol. 2019;43(5):533-541.
42. Petta S, Miele L, Bugianesi E, Camma C, Rosso C, Boccia S, et al. Glucokinase regulatory protein gene polymorphism affects liver fibrosis in non-alcoholic fatty liver disease. PLoS One 2014; 9(2):e87523.
43. Zain SM, Mohamed Z, Mohamed R. Common variant in the glucokinase regulatory gene rs780094 and risk of nonalcoholic fatty liver disease: a meta-analysis. J Gastroenterol Hepatol. 2015;30(1):21-27.
44. Kawaguchi T, Shima T, Mizuno M, Mitsumoto Y, Umemura A, Kanbara Y, et al. Risk estimation model for nonalcoholic fatty liver disease in the Japanese using multiple genetic markers. PLoS ONE. 2018;13(1):e0185490.
45. Mancina RM, Dongiovanni P, Petta S, Pingitore P, Meroni M, Rametta R, et al. The MBOAT7-TMC4 variant rs641738 increases risk of nonalcoholic fatty liver disease in individuals of European descent. Gastroenterology. 2016;150(5):1219-1230.
46. Donati B, Dongiovanni P, Romeo S, Meroni M, McCain M, Miele L, et al. MBOAT7 rs641738 variant and hepatocellular carcinoma in non-cirrhotic individuals. Sci Rep. 2017;7(1):4492.
47. Eslam M, Valenti L, Romeo S. Genetics and epigenetics of NAFLD and NASH: clinical impact. J Hepatol. 2018;68(2):268-279.
48. Gellert-Kristensen H, Richardson TG, Smith GD, Nordestgaard BG, Tybjærg-Hansen A,Stender S. Combined effect of PNPLA3, TM6SF2, and HSD17B13 variants on risk of cirrhosis and hepatocellular carcinoma in the general population. Hepatology 2020;72(3):845-856.
49. Trepo E, Valenti L. Update on NAFLD genetics: from new variants to the clinic. J Hepatol. 2020;72(6):1196-1209.
50. Schwartz B, Rajagopal V, Smith C, Cohick E, Whissell G, Gamboa M, et al. Discovery and targeting of the signaling controls of PNPLA3 to effectively reduce transcription, expression, and function in pre-clinical NAFLD/NASH settings. Cells. 2020;9(2):2247.
51. Zeng F, Zhang Y, Han X, Zeng M, Gao Y, Weng J. Predicting non-alcoholic fatty liver disease progression and immune deregulations by specific gene expression patterns. Front Immunol. 2021;11(1):609900