in vivo *34*: 3309-3313 (2020)
doi:10.21873/invivo.12169

Association of Genetic Polymorphisms With Hepatitis C Virus-related Liver Cirrhosis in Japan

SHINYA KAMIMURA, AKINORI TAMURA, TOMOTAKA ISHII, TATSUO KANDA and MITSUHIKO MORIYAMA

Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

Abstract. *Background/Aim: Hepatitis C virus (HCV) infection is an important health problem in the direct-acting antivirals-era. HCV causes life-threatening diseases, such as cirrhosis and hepatocellular carcinoma. Our aim was to examine whether certain single-nucleotide polymorphisms (SNPs) are associated with the prevalence of HCV infections progressing to cirrhosis in the Japanese population by a genome-wide association study-based approach. Materials and Methods: We used DNA extracted from blood specimens of Japanese subjects with the establishment of the BioBank Japan project. Results: We observed statistically significant differences in the frequency of 4 SNPs (rs1989972, rs2293766, rs1877033 and rs4805439) between anti-HCV-positive cirrhotic patients and controls. Conclusion: Four SNPs are associated with susceptibility to cirrhosis among HCV-infected Japanese subjects, while further studies with cohorts other than those sourced from BioBank Japan, must be conducted.*

Hepatitis C virus (HCV) infection is an important health problem in Japan and the United States, although direct-acting antivirals (DAAs) against HCV have been introduced (1, 2). HCV infection causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (HCC) for hepatic manifestations and cryoglobulinemia, lymphoma, insulin resistance, type 2 diabetes and chronic kidney diseases for extrahepatic manifestations (3, 4). HCC occurs in ~7% of patients with cirrhosis per year, although HCC occurs in less than 1% of patients with non-advanced liver fibrosis per year (3).

Correspondence to: Tatsuo Kanda, MD, Ph.D., Associate Professor, Division of Gastroenterology and Hepatology, Department of Medicine, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan. Tel: +81 339728111, Fax: +81 339568496, e-mail: kanda.tatsuo@nihon-u.ac.jp

Key Words: BioBank Japan, GWAS, HCV, SNP, TGFBI.

Patients infected with HCV do not always develop cirrhosis (5). It is well known that the frequencies of cirrhosis and HCC are different among different races (6, 7). These facts suggest that certain single-nucleotide polymorphisms (SNPs) affect the development of hepatic fibrosis in patients with HCV infection. In the United States, subjects with chronic hepatitis C carrying the DEAD box polypeptide 5 (DDX5) minor allele or DDX5- DNA polymerase gamma 2, accessory subunit (POLG2) haplotypes are at increased risk of developing advanced fibrosis, whereas those carrying the carnitine palmitoyltransferase 1A (CPT1A) minor allele are at decreased risk (8).

It has been reported that compared to a major, wild-type (WT) CC allele, the minor allele rs4986791 in the TLR4 gene encoding the T399I change, confers protection against fibrosis progression, along with another highly cosegregated SNP (rs4986790) located at codon position 299 (p.D299G) (9), although the TLR4 SNPs (rs4986790 and rs4986791) are uniformly distributed in Japanese patients (10).

In the present study, we examined whether certain SNPs are associated with the prevalence of HCV infections progressing to cirrhosis in the Japanese population by a genome-wide association study (GWAS)-based approach. We used DNA extracted from blood specimens of Japanese subjects with the establishment of the BioBank Japan project that stores and maintains a number of annotated liver disease cases (11). We observed that four SNPs are associated with susceptibility to cirrhosis among HCV infected Japanese subjects.

Materials and Methods

Subjects, DNA preparation and SNP genotyping. Study 1. We selected patients with cirrhosis (n=195; male/female: 107/88; age, 65±9 years) and control subjects who did not have liver diseases (n=1,553; male/female: 889/664; age, 61±18 years). The HCV infection status of patients with cirrhosis was: 80, positive; 25, negative; and 90, unknown. Control subjects were also enrolled as patients with diseases other than liver diseases in BioBank Japan (11). Patients who had cirrhosis were also excluded from these controls. A GWAS was performed with high-density oligonucleotide arrays (Perlegen Sciences, Santa Clara, CA, USA) for SNP genotyping.

Table I. *Twenty-nine highly ranked single-nucleotide polymorphisms (SNPs) which were associated with cirrhosis.*

SNP	Chromosome	Allele (*p*-Value)	Dominant model (*p*-Value)	Recessive model (*p*-Value)
rs17380837	12	<0.001	<0.001	<0.001
rs4419128	18	<0.001	<0.001	0.3570
rs2114196	8	<0.001	<0.001	–1.000
rs3813573	15	<0.001	<0.001	<0.001
rs3783728	14	<0.001	1.000	<0.001
rs1143637	2	<0.001	0.1672	<0.001
rs1989972	5	<0.001	<0.001	<0.001
rs1443899	8	<0.001	<0.001	<0.001
rs2493035	6	<0.001	<0.001	0.0683
rs4954144	2	<0.001	<0.001	0.0227
rs2116287	10	<0.001	<0.001	0.0055
rs6555491	5	<0.001	<0.001	0.1647
rs1874361	1	<0.001	0.0066	<0.001
rs1877033	4	<0.001	0.1650	<0.001
rs829523	3	<0.001	0.0013	0.1153
rs2279674	4	<0.001	0.0029	0.0069
rs1157977	6	<0.001	<0.001	0.0081
rs3737964	1	0.0012	0.0011	0.3832
rs349765	5	0.0014	0.0013	–1.000
rs4805439	19	0.0017	0.0093	0.0106
rs4663603	2	0.0026	0.0050	0.2728
rs10500651	11	0.0030	0.0114	0.0103
rs2293766	7	0.0034	0.0016	0.1694
rs674993	3	0.0040	0.0545	0.0105
rs16987220	2	0.0043	0.0391	0.0126
rs6511152	19	0.0045	0.0270	0.0168
rs2036100	1	0.0051	0.0174	0.0249
rs9380236	6	0.0080	0.0150	0.0364
rs10197150	2	0.0084	0.1534	0.0087

Table II. *Genotyping results of 29 single-nucleotide polymorphisms (SNPs) in patients with cirrhosis.*

SNP	Chromosome	Allele[#] [1/2]	[1/1]	[1/2]	[2/2]	Frequency [1][##]
rs17380837	12	C/T	40	36	4	0.725
rs4419128	18	A/G	0	5	75	0.031
rs2114196	8	C/T	12	39	4	0.394
rs3813573	15	G/A	31	38	11	0.625
rs3783728	14	T/C	73	6	1	0.950
rs1143637	2	G/A	74	6	0	0.963
rs1989972	5	C/A	12	33	35	0.362
rs1443899	8	T/C	57	21	2	0.844
rs2493035	6	T/C	45	27	5	0.760
rs4954144	2	T/G	71	8	1	0.938
rs2116287	10	T/C	4	40	35	0.304
rs6555491	5	T/C	73	7	0	0.956
rs1874361	1	G/T	6	36	36	0.308
rs1877033	4	T/C	66	14	0	0.913
rs829523	3	C/T	72	6	1	0.949
rs2279674	4	G/T	34	38	6	0.679
rs1157977	6	C/A	52	24	3	0.810
rs3737964	1	G/A	62	16	1	0.886
rs349765	5	A/G	77	3	0	0.981
rs4805439	19	A/G	2	17	53	0.146
rs4663603	2	T/C	77	3	0	0.981
rs10500651	11	T/G	70	10	0	0.933
rs2293766	7	C/T	13	28	35	0.459
rs674993	3	A/G	36	34	4	0.716
rs16987220	2	G/A	46	31	3	0.789
rs6511152	19	C/G	26	37	16	0.564
rs2036100	1	G/C	41	33	6	0.719
rs9380236	6	A/G	59	21	0	0.869
rs10197150	2	T/C	23	42	9	0.595

[#]Ancestral allele; [##]frequency [1]=allele 1/(allele 1+allele 2).

Study 2. We selected patients with cirrhosis (n=753; male/female: 431/322; age, 63±10.7 years) and control subjects who did not have liver diseases (n=1,358; male/female: 738/620; age, 59±13.5 years). The HCV infection status of patients with cirrhosis was: 95, positive; 110, negative; and 548, unknown. Control subjects were enrolled as patients with diseases other than liver diseases in BioBank Japan (11). Patients who had cirrhosis were also excluded from these controls. A GWAS was performed with a GeneChip SNP array (Affymetrix, Santa Clara, CA, USA) for SNP genotyping.

Study 3. We performed 29 SNP analyses of anti-HCV-positive patients with cirrhosis (n=80; male/female: 45/35; age, 65±11 years). DNA samples were genotyped with a TaqMan SNP genotyping assay (Applied Biosystems Inc, Foster City, CA, USA) using an ABI 7500 Fast real-time PCR system, according to the manufacturer's recommended protocols (10). The PCR was performed as follows: 95˚C for 10 min, followed by 55 cycles of 95˚C for 15 sec and 60˚C for 1 min. The subjects did not have HCC at blood sample collection. SNP alleles of Japanese healthy subjects (HapMap-JPT) were used as controls from the International HapMap Project (https://hapmap.ncbi.nlm.nih.gov/index.html) (12).

BioBank Japan was launched in 2003, establishing a large Japanese patient-oriented biobank to contribute to the implementation of personalized medicine (11). All patients participating in the present study provided written informed consent and the study protocol was approved by the ethics committees of RIKEN Yokohama Institute and of each participating institution. The study protocol for study 3 was also approved by the Ethics Committee of Nihon University School of Medicine (i-1) and conformed to the ethical guidelines of the Declaration of Helsinki.

Statistical analysis. Statistical analyses were performed using a Fisher's exact test. $p<0.05$ was considered as a statistically significant difference. Statistical analysis was performed with SPSS v.15 (SPSS Inc, Chicago, IL, USA). We analyzed the differences between the case and control groups in terms of the distribution of genotypes with an allelic model by using a Cox's proposal hazards model analysis.

Results

Candidate SNPs associated with cirrhosis selected by the GWAS. A GWAS was performed with high-density oligonucleotide arrays (Perlegen Sciences, Santa Clara, CA, USA), resulting in the selection of 233,820 SNPs for

Table III. *Frequencies of single-nucleotide polymorphism (SNP) rs1989972 between anti-hepatitis C virus (HCV)-positive subjects with liver cirrhosis (LC) and controls.*

Allele	LC	Control	OR	95% CI	*p*-Value
C/C	33	22	–	–	0.048#
C/A	35	54			
A/A	12	10			
C/C	33	22	2.04	1.06-3.94	0.047#
Others	47	64			
A/A	12	10	0.75	0.3-1.84	0.648
Others	68	76			
Allele C	104	98	1.33	0.86-2.07	0.264
Allele A	59	74			

OR, Odds ratio; 95%CI, 95% confidence interval; #$p<0.05$, statistically significant difference by Fisher's exact test.

Table V. *Frequencies of single-nucleotide polymorphism (SNP) rs1877033 between anti-hepatitis C virus (HCV)-positive subjects with liver cirrhosis (LC) and controls.*

Allele	LC	Control	OR	95% CI	*p*-Value
TC/C	0	0	–	–	0.014#
C/T	14	1			
T/T	66	42			
C/C	0	0	–	–	1
Others	80	43			
T/T	66	42	8.91	1.13-70.3	0.018#
Others	14	1			
Allele C	14	1	8.15	1.05-63.1	0.022#
Allele T	146	85			

OR, Odds ratio; 95%CI, 95% confidence interval; #$p<0.05$, statistically significant difference by Fisher's exact test.

Table IV. *Frequencies of single-nucleotide polymorphism (SNP) rs2293766 between anti-hepatitis C virus (HCV)-positive subjects with liver cirrhosis (LC) and controls.*

Allele	LC	Control	OR	95% CI	*p*-Value
T/T	33	25	–	–	0.085
T/C	28	43			
C/C	13	18			
T/T	35	25	2.08	1.09-3.98	0.034#
Others	41	61			
C/C	13	18	1.28	0.58-2.83	1
Others	63	68			
Allele T	98	93	1.54	0.99-2.41	0.149
Allele C	54	79			

OR, Odds ratio; 95%CI, 95% confidence interval; #$p<0.05$, statistically significant difference by Fisher's exact test.

Table VI. *Frequencies of single-nucleotide polymorphism (SNP) rs4805439 between anti-hepatitis C virus (HCV)-positive subjects with liver cirrhosis (LC) and controls.*

Allele	LC	Control	OR	95% CI	*p*-Value
G/G	53	24	–	–	0.052
G/A	17	15			
A/A	2	5			
G/G	53	24	2.32	1.05-5.13	0.044#
Others	19	20			
A/A	70	39	3.59	0.63-20.5	0.103
Others	2	4			
Allele G	123	63	2.32	1.21-4.47	0.017#
Allele A	21	25			

OR, Odds ratio; 95%CI, 95% confidence interval; #$p<0.05$, statistically significant difference by Fisher's exact test.

genotyping, at the first stage. A GWAS was performed with a GeneChip SNP array (Affymetrix, Santa Clara, CA, USA) including 233,820 SNPs, resulting in the selection of 2,670 SNPs for genotyping, at the second stage. Finally, we selected 29 highly ranked SNPs as candidates associated with cirrhosis (Table I).

Association of SNPs with HCV infection and cirrhosis in Japanese subjects. Table II shows the frequencies of these SNPs in 80 anti-HCV-positive patients with cirrhosis. We observed the statistically significant differences in the frequencies of 4 SNPs (rs1989972, rs2293766, rs1877033 and rs4805439) between anti-HCV-positive cirrhotic patients and controls (Tables II-VI). Two SNPs (rs1989972 and rs2293766) were located within an intron of transforming growth factor beta induced (TGFBI) and zonadhesin (ZAN), respectively. The other 2 SNPs (rs1877033 and rs4805439) were located outside the protein coding regions. Together, we identified four loci conferring susceptibility to cirrhosis among HCV-infected subjects.

Discussion

In the present study, we used the collection of GWAS data and DNA from HCV-infected cirrhotic individuals and controls from BioBank Japan (11) and used the data of SNP alleles of Japanese healthy subjects (HapMap-JPT) as a control from the International HapMap Project (12). We identified the involvement of four loci in conferring susceptibility to cirrhosis among HCV-infected subjects.

TGFBI is one of the useful markers to diagnose hepatitis B virus (HBV)-related cirrhosis (13). Plasma proteome profiling revealed a strong association between TGFBI, dipeptidyl peptidase 4 (DPP4), alanyl aminopeptidase, membrane (ANPEP), polymeric immunoglobulin receptor (PIGR) and apolipoprotein E (APOE) and nonalcoholic fatty

liver disease (NAFLD)-derived cirrhosis (14). TGFBI drives the proliferation of hepatocytes (15). TGFB-induced protein TGFBI is a collagen-associated protein associated with hepatic fibrogenesis (16).

Fibroblast growth factor 19 (FGF-19) treatment increased the expression of proteins known to drive proliferation [TGFBI, vascular cell adhesion molecule-1 (VCAM-1), Annexin A2 and high density lipoprotein binding protein (HDLBP)] (15). It is well known that FGF is also a potent angiogenic molecule involved in HCC progression (17). Recently, Kim *et al*. reported that FGF-2 and its receptor SNPs are associated with the survival of patients with HBV-related HCC (18). Although rs1989972 is located within an intron of TGFBI, we observed a weak association between rs1989972 C/C and patients with HCV infection and cirrhosis (Table III).

ZAN is a mosaic-type protein that localizes to the apical head of spermatozoa (19). The association between ZAN and hepatic fibrosis is unclear. Although rs2293766 is located within the ZAN-coding region, we observed that an association between rs2293766 T/T and patients with HCV infection and cirrhosis (Table IV).

Two SNPs (rs1877033 and rs4805439) were located outside the protein-coding regions, and these SNPs are associated with patients with HCV infection and cirrhosis (Table V and VI). It has been reported that noncoding RNAs (such as microRNAs and long noncoding RNAs) are involved in hepatic fibrosis (20, 21). Further studies are needed.

Although treatment with DAAs can reduce Model for End-Stage Liver Disease (MELD) and Child-Pugh-Turcotte (CPT) scores in patients with HCV infection and decompensated cirrhosis, many HCV-infected patients with decompensated cirrhosis still die or require liver transplantation (22). It is important to predict reversible or irreversible hepatic fibrosis in HCV-infected patients with cirrhosis. SNPs are thought to be non-modifiable factors that affect disease activity or the efficacy of treatment (23, 24).

BioBank Japan project is a large patient-oriented cohort: DNA, serum samples and clinical information which will be used for further studies (25). In the present study, we demonstrated an overview of the patients with susceptibility to HCV-related cirrhosis in this project. However, there are some limitations of the present study. Our study is not a prospective study, and we should also perform a study of cohorts other than those sourced from BioBank Japan. In conclusion, we elucidated that four SNPs are associated with susceptibility to cirrhosis among HCV-infected Japanese subjects.

Conflicts of Interest

The Authors declare no conflicts of interest with regards to the present study.

Authors' Contributions

S.K., A.T. and M.M. conceptualized the study., collected data, carried out the analysis. S.K., A.T., T.I., T.K. and M.M. drafted the initial manuscript and revised the manuscript. All Authors approved the final manuscript.

Acknowledgements

Authors thank Prof. Shiro Maeda, Laboratory for Endocrinology, Metabolism and Kidney Diseases, RIKEN Center for Integrative Medical Sciences, Yokohama 230-0045, Japan and Prof. Naoya Kato, Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, University of Tokyo, Tokyo, Japan, for valuable discussion.

References

1 Tanaka J, Akita T, Ko K, Miura Y, Satake M and Epidemiological Research Group on Viral Hepatitis and its Long-term Course, Ministry of Health, Labour and Welfare of Japan: Countermeasures against viral hepatitis B and C in Japan: an epidemiological point of view. Hepatol Res *49(9)*: 990-1002, 2019. PMID: 31364248. DOI: 10.1111/hepr.13417

2 Thrift AP, El-Serag HB and Kanwal F: Global epidemiology and burden of HCV infection and HCV-related disease. Nat Rev Gastroenterol Hepatol *14(2)*: 122-132, 2017. PMID: 27924080. DOI: 10.1038/nrgastro.2016.176

3 Takano S, Yokosuka O, Imazeki F, Tagawa M and Omata M: Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. Hepatology *21(3)*: 650-655, 1995. PMID: 7875662.

4 Omata M, Kanda T, Yu ML, Yokosuka O, Lim SG, Jafri W, Tateishi R, Hamid SS, Chuang WL, Chutaputti A, Wei L, Sollano J, Sarin SK, Kao JH and McCaughan GW: APASL consensus statements and management algorithms for hepatitis C virus infection. Hepatol Int *6(2)*: 409-435, 2012. PMID: 26201405. DOI: 10.1007/s12072-012-9342-y

5 Seeff LB: Natural history of hepatitis C. Hepatology *26(3 Suppl 1)*: 21S-28S, 1997. PMID: 9305659. DOI: 10.1002/hep.510260704

6 Turner BJ, Wang CP, Melhado TV, Bobadilla R, Jain MK and Singal AG: Significant increase in risk of fibrosis or cirrhosis at time of HCV diagnosis for Hispanics with diabetes and obesity compared with other ethnic groups. Clin Gastroenterol Hepatol *17(7)*: 1356-1363, 2019. PMID: 30529733. DOI: 10.1016/j.cgh.2018.11.059

7 Makarova-Rusher OV, Altekruse SF, McNeel TS, Ulahannan S, Duffy AG, Graubard BI, Greten TF and McGlynn KA: Population attributable fractions of risk factors for hepatocellular carcinoma in the United States. Cancer *122(1)*: 1757-1765, 2016. PMID: 26998818. DOI: 10.1002/cncr.29971

8 Huang H, Shiffman ML, Cheung RC, Layden TJ, Friedman S, Abar OT, Yee L, Chokkalingam AP, Schrodi SJ, Chan J, Catanese JJ, Leong DU, Ross D, Hu X, Monto A, McAllister LB, Broder S, White T, Sninsky JJ and Wright TL: Identification of two gene variants associated with risk of advanced fibrosis in patients with chronic hepatitis C. Gastroenterology *130(6)*: 1679-1687, 2006. PMID: 16697732. DOI: 10.1053/j.gastro.2006.02.032

9 Guo J, Loke J, Zheng F, Hong F, Yea S, Fukata M, Tarocchi M, Abar OT, Huang H, Sninsky JJ and Friedman SL: Functional linkage of cirrhosis-predictive single nucleotide polymorphisms of toll-like receptor 4 to hepatic stellate cell responses. Hepatology *49(3)*: 960-968, 2009. PMID: 19085953. DOI: 10.1002/hep.22697

10 Nakamura M, Kanda T, Nakamoto S, Miyamura T, Jiang X, Wu S and Yokosuka O: No correlation between PNPLA3 rs738409 genotype and fatty liver and hepatic cirrhosis in Japanese patients with HCV. PLoS One *8(12)*: e81312, 2013. PMID: 24349054. DOI: 10.1371/journal.pone.0081312

11 Nagai A, Hirata M, Kamatani Y, Muto K, Matsuda K, Kiyohara Y, Ninomiya T, Tamakoshi A, Yamagata Z, Mushiroda T, Murakami Y, Yuji K, Furukawa Y, Zembutsu H, Tanaka T, Ohnishi Y, Nakamura Y, BioBank Japan Cooperative Hospital Group and Kubo M: Overview of the BioBank Japan project: study design and profile. J Epidemiol *27(3S)*: S2-S8, 2017. PMID: 28189464. DOI: 10.1016/j.je.2016.12.005

12 International HapMap Consortium: The International HapMap Project. Nature *426(6968)*: 789-796, 2003. PMID: 14685227. DOI: 10.1038/nature02168

13 Lu YY, Chen QL, Guan Y, Guo ZZ, Zhang H, Zhang W, Hu YY and Su SB: Transcriptional profiling and co-expression network analysis identifies potential biomarkers to differentiate chronic hepatitis B and the caused cirrhosis. Mol Biosyst *10(5)*: 1117-1125, 2014. PMID: 24599568. DOI: 10.1039/c3mb70474b

14 Niu L, Geyer PE, Wewer Albrechtsen NJ, Gluud LL, Santos A, Doll S, Treit PV, Holst JJ, Knop FK, Vilsbøll T, Junker A, Sachs S, Stemmer K, Müller TD, Tschöp MH, Hofmann SM and Mann M: Plasma proteome profiling discovers novel proteins associated with non-alcoholic fatty liver disease. Mol Syst Biol *15(3)*: e8793, 2019. PMID: 30824564. DOI: 10.15252/msb.20188793

15 Massafra V, Milona A, Vos HR, Burgering BM and van Mil SW: Quantitative liver proteomics identifies FGF19 targets that couple metabolism and proliferation. PLoS One *12(2)*: e0171185, 2017. PMID: 28178326. DOI: 10.1371/journal.pone.0171185

16 Decaris ML, Emson CL, Li K, Gatmaitan M, Luo F, Cattin J, Nakamura C, Holmes WE, Angel TE, Peters MG, Turner SM and Hellerstein MK: Turnover rates of hepatic collagen and circulating collagen-associated proteins in humans with chronic liver disease. PLoS One *10(4)*: e0123311, 2015. PMID: 25909381. DOI: 10.1371/journal.pone.0123311

17 Kin M, Sata M, Ueno T, Torimura T, Inuzuka S, Tsuji R, Sujaku K, Sakamoto M, Sugawara H, Tamaki S and Tanikawa K: Basic fibroblast growth factor regulates proliferation and motility of human hepatoma cells by an autocrine mechanism. J Hepatol *27(4)*: 677-687, 1997. PMID: 9365044. DOI: 0.1016/S0168-8278(97)80085-2

18 Kim SS, Eun JW, Cho HJ, Lee HY, Seo CW, Noh CK, Shin SJ, Lee KM, Cho SW and Cheong JY: Effect of fibroblast growth factor-2 and its receptor gene polymorphisms on the survival of patients with hepatitis B virus-associated hepatocellular carcinoma. Anticancer Res *39(4)*: 2217-2226, 2019. PMID: 30952770. DOI: 10.21873/anticanres.13337

19 Herlyn H and Zischler H: The molecular evolution of sperm zonadhesin. Int J Dev Biol *52(5-6)*: 781-790, 2008. PMID: 18649290. DOI: 10.1387/ijdb.082626hh

20 Fu N, Niu X, Wang Y, Du H, Wang B, Du J, Li Y, Wang R, Zhang Y, Zhao S, Sun D, Qiao L and Nan Y: Role of lncrna-activated by transforming growth factor beta in the progression of hepatitis C virus-related liver fibrosis. Discov Med *22(119)*: 29-42, 2016. PMID: 27585228.

21 Devhare PB, Sasaki R, Shrivastava S, Di Bisceglie AM, Ray R and Ray RB: Exosome-mediated intercellular communication between hepatitis C virus-infected hepatocytes and hepatic stellate cells. J Virol *91(6)*: e02225-16, 2017. PMID: 28077652. DOI: 10.1128/JVI.02225-16

22 El-Sherif O, Jiang ZG, Tapper EB, Huang KC, Zhong A, Osinusi A, Charlton M, Manns M, Afdhal NH, Mukamal K, McHutchison J, Brainard DM, Terrault N and Curry MP: Baseline factors associated with improvements in decompensated cirrhosis after direct-acting antiviral therapy for hepatitis C virus infection. Gastroenterology *154(8)*: 2111-2121.e8, 2018. PMID: 29535028. DOI: 10.1053/j.gastro.2018.03.022

23 Miki D, Ochi H, Hayes CN, Abe H, Yoshima T, Aikata H, Ikeda K, Kumada H, Toyota J, Morizono T, Tsunoda T, Kubo M, Nakamura Y, Kamatani N and Chayama K: Variation in the DEPDC5 locus is associated with progression to hepatocellular carcinoma in chronic hepatitis C virus carriers. Nat Genet *43(8)*: 797-800, 2011. PMID: 21725309. DOI: 10.1038/ng.876

24 Tanaka Y, Nishida N, Sugiyama M, Kurosaki M, Matsuura K, Sakamoto N, Nakagawa M, Korenaga M, Hino K, Hige S, Ito Y, Mita E, Tanaka E, Mochida S, Murawaki Y, Honda M, Sakai A, Hiasa Y, Nishiguchi S, Koike A, Sakaida I, Imamura M, Ito K, Yano K, Masaki N, Sugauchi F, Izumi N, Tokunaga K and Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. Nat Genet *41(10)*: 1105-1109, 2009. PMID: 19749757. DOI: 10.1038/ng.449

25 Ukawa S, Okada E, Nakamura K, Hirata M, Nagai A, Matsuda K, Yamagata Z, Kamatani Y, Ninomiya T, Kiyohara Y, Muto K, Kubo M, Nakamura Y; BioBank Japan Cooperative Hospital Group and Tamakoshi A: Characteristics of patients with liver cancer in the BioBank Japan project. J Epidemiol *27(3S)*: S43-S48, 2017. PMID: 28214185. DOI: 10.1016/j.je.2016.12.007

Received June 30, 2020
Revised July 16, 2020
Accepted July 17, 2020