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TOPIC HIGHLIGHT

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Interleukin 28B genetic polymorphism and hepatitis B virus infection

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Abstract

Interleukin (IL) 28B genetic polymorphism is significantly associated with the sustained virological response rate in patients with chronic hepatitis C treated with pegylated interferon-α (PEG-IFN) plus ribavirin and with spontaneous hepatitis C virus clearance. However, a consensus on the relationship between IL28B genetic polymorphism and the favorable outcome of chronic hepatitis B virus infection defined by hepatitis B e antigen seroconversion, and/or hepatitis B surface antigen seroclearance in patients treated with interferon or PEG-IFN has not been reached. Several reports failed to show a positive association, while some studies demonstrated a positive association in certain subject settings. More prospective studies including large cohorts are needed to determine the possible association between IL28B genetic polymorphism and the outcome of interferon or PEG-IFN treatment for chronic hepatitis B.

Key words: Interleukin 28B; Polymorphism; Hepatitis B virus; Interferon; Pegylated interferon

Core tip: An association between interleukin (IL) 28B genetic polymorphism and sustained virological response rate in patients with chronic hepatitis C treated with pegylated interferon-α and ribavirin or spontaneous hepatitis C virus clearance has been established. However, the association between IL28B genetic polymorphism and hepatitis B virus infection remains unclear. We discuss this topic and summarize the available clinical data.

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INTRODUCTION

Recent advances in molecular biology have enabled us to discover not only various factors regarding pathogens, but also regarding hosts which may influence the fate, character, mode of onset and natural or therapeutic outcome of various disorders. One such example is a genome-wide analysis of sequence. Such progress is also obvious in the research field of gastroenterology and hepatology. For example, the discovery of an association between single nucleotide polymorphism (SNP) at or near the interleukin 28B (*IL28B*) gene and the sustained virological response (SVR) rate with pegylated interferon-α (PEG-IFN) plus ribavirin (RBV) treatment for chronic hepatitis C (CH-C)[1-3]. Subsequent studies confirmed an association between *IL28B* and spontaneous hepatitis C virus (HCV) clearance[4,5]. The *IL28B* genetic polymorphism also accounts for the racial difference in the SVR rate with PEG-IFN/RBV treatment for CH-C[1].

Recently, a possible association between *IL28B* genetic polymorphism and hepatitis B virus (HBV) infection has become a target of interest. It is known that 240 million

individuals are chronically infected with HBV worldwide[6], with the majority in the Asia-Pacific region[7]. An association between *IL28B* genetic polymorphism and the rate of hepatitis B e antigen (HBeAg) seroconversion and/or hepatitis B surface antigen (HBsAg) seroclearance with PEG-IFN treatment has been intensively discussed recently.

Here we summarize and discuss the possible association between *IL28B* genetic polymorphism and the favorable outcome of chronic HBV infection defined by HBeAg seroconversion and/or HBsAg seroclearance in patients with chronic hepatitis B (CH-B) treated by PEG-IFN with or without nucleoside analogues.

FACTS ON *IL28B*

IL28B is a class Ⅱ cytokine receptor ligand related to type I interferons. These ligands play a critical role in response to microbial challenge and activate the JAK/STAT signaling system and show anti-viral activity by inducing interferon-stimulated genes (ISG)[8]. *IL28B* is located on the long arm of chromosome 19 and spans about 1.5 kilo base pairs. It encodes interferon λ3 (IFN λ3), one of the type Ⅲ IFNs, while *IL29* and *IL28A* encode other type Ⅲ IFNs, namely IFN λ1 and λ2.

It is unknown why *IL28B* (namely IFN λ3) genetic polymorphism influences the SVR in PEG-IFN/RBV therapy for CH-C as described above. Gene expression studies using peripheral blood mononuclear cells revealed that *IL28B* gene expression was lower in individuals carrying minor alleles[2,3]. In contrast, there is no difference in hepatic *IL28B* gene expression according to haplotypes, although pretreatment intrahepatic ISG expressions are higher in individuals carrying minor alleles[9,10]. These results may support the previously reported findings that already elevated ISG gene expression before treatment was significantly related to poor viral eradication rate since externally administered PEG-IFN did not fully stimulate ISG[11,12].

Type Ⅲ IFN is a major component of the innate immune system of liver cells. HCV infection studies in primary human fetal liver cell cultures[13] revealed that cell culture-induced HCV evoked expression of type Ⅲ (λ) IFNs and of ISGs, while low expression of type I IFNs (IFN α and β) was observed. Higher levels of viral replication were associated with greater induction of ISGs and IFNλ. It was shown in 2005 that IFNλ inhibited HBV replication in a differentiated murine hepatocyte cell line as well as replication of a subgenomic and a full-length genomic HCV replicon in Huh7 cells[14]. IFN-α and IFNλ3 in combination showed synergistic anti-HCV activity in the HCV 1b and 2a replicon system[15]. The humanized livers of chimeric mice exhibited increased expression at the mRNA and protein level of human IFNλs, following treatment with a hepatotropic cationic liposome and a synthetic double-stranded RNA analog[16] resulting in a strong antiviral effect on HBV and HCV. With regard to the possibility of IFNλ as a therapeutic agent for CH-C, a phase 1b trial revealed that weekly PEG-IFN-λ with or without daily RBV for 4 wk was associated with clear antiviral activity across a broad range of doses in patients with CH-C[17].

As another source of IFN-λ in liver, human type 2 myeloid dendritic cells, or human blood dendritic cell antigen 3-positive cells instead of hepatocytes were recently reported to be a potent producer of IFN-λ in response to HCV[18,19].

POSSIBLE ASSOCIATION BETWEEN *IL28B* GENETIC POLYMORPHISM AND SPONTANEOUS HBV RECOVERY OR OUTCOME OF PEG-IFN TREATMENT FOR CH-B

The first study concerning *IL28B* and HBV infection was reported in 2010, the following year it was discovered that this genetic polymorphism was strongly associated with the SVR rate in patients with CH-C treated with PEG/RBV. In this report, C-C genotype of rs12979860 was not associated with HBV recovery (OR = 0.99)[20]. Two subsequent reports in 2011[21,22] also failed to show the possible association, although one revealed an association between genotype, allele and haplotype frequencies of *IL28B* and both aminotransferase levels and HBV DNA[21]. In 2012, the first report that determined a positive association between *IL28B* genetic polymorphism and chronic HBV infection was published[23]. *IL28B* genotype was significantly associated with HBeAg seroconversion at the end of PEG-IFN treatment ($P < 0.01$), the adjusted odds ratio for seroconversion was 3.16 ($P = 0.013$) for AA *vs* AG/GG at rs12980275 after adjustment for HBV genotype, age, levels of HBV DNA and alanine aminotransferase, and PEG-IFN and a nucleoside analogue-lamivudine combination therapy. *IL28B* genotype was independently associated with an increased probability of HBeAg seroconversion during long-term follow-up (adjusted HR = 2.14, $P = 0.018$ by Cox regression analysis). Similar results were obtained for rs12979860. *IL28B* genotype was also associated with HBsAg clearance (HR = 3.47, $P = 0.042$). Thus, the authors concluded that polymorphisms near *IL28B* were independently associated with serologic response to PEG-IFN in patients with HBeAg-positive chronic hepatitis B.

Another report published in 2012[24] also demonstrated a possible association between IL28B and HBeAg-positive CH-B in a Chinese Han population, while another 3 reports published in the same year[25-27] concluded that *IL28B* was not significantly related to the outcome of patients with CH-B who were treated with PEG-IFN. Three SNPs in the *IL28B* gene (rs12979869C/T, rs8099917G/T and rs12980275G/A) were examined in 330 subjects [including 154 HBV-related hepatocellular carcinoma (HCC) patients, 86 non-HCC patients with CH-B, 43 HBV self-limited infections and 47 healthy controls][28]. In conclusion, the *IL28B* rs12979860C/T polymorphism might affect susceptibility to chronic HBV infection and progression of HCC. In another report, the

Table 1 Possible association between interleukin 28B genetic polymorphism and the effect of interferon-α and/or pegylated interferon-α, or spontaneous hepatitis B e antigen and/or hepatitis B surface antigen clearance in hepatitis B virus infection

No.	Year	Ref.	Targeted SNPs	Subject settings	HBe	Result	Comments
1	2010	Martin *et al*[20]	rs12979860	226 HBV persistence, 384 HBV recovery	ND	Negative	C/C genotype of rs12979860 was not associated with HBV recovery (OR = 0.99)
2	2011	Li *et al*[21]	rs12979860, rs12980275, rs8099917	203 chronic HBV infection, 203 self-limited HBV infection, 203 individuals negative for all HBV seromarkers (Chinese Han population)	ND	Negative	
3	2011	Tseng *et al*[22]	IL28B regions	115 HBeAg-positive chronic hepatitis B patients	Positive	Negative	
4	2012	Sonneveld *et al*[23]	rs12980275, rs12979860	205 HBeAg-positive patients who were treated with PEG-IFN (Europeans and Asians)	Positive	Positive	IL28B genotype was significantly associated with HBeAg seroconversion at the end of treatment ($P < 0.001$, OR = 3.16), during long-term follow up (HR = 2.14), or with HBsAg seroclearance (HR = 3.47)
5	2012	Wu *et al*[24]	rs8099917	512 HBeAg positive chronic hepatitis B patients (Han Chinese) were treated with pegylated interferon a-2a ± nucleoside analogues	Positive	Positive	The frequency of G allele of rs8099917 was significantly higher in the response group than in the non-response group (8.3% *vs* 3.9%, $P = 0.003$, OR = 0.44, 95%CI: 0.25-0.79). The genotype distributions of this SNP also differed significantly between the two groups ($P = 0.003$)
6	2012	de Niet *et al*[25]	rs12979860	95 chronic hepatitis B patients who were treated with PEG-IFN and adefovir for 1 yr and who had 15% HBsAg loss (overall)	Positive and negative	Negative	
7	2012	Peng *et al*[26]	rs12979860	651 HBV persistent infection (387 with liver cirrhosis, 264 without cirrhosis), 226 healthy individuals who recovered from HBV infection	ND	Negative	No association with clearance of HBsAg, HBeAg, HBV DNA level, apparent hepatitis onset and liver cirrhosis ($P > 0.05$)
8	2013	Lampertico *et al*[31]	rs12979860	101 HBeAg-negative patients (92% genotype D) with compensated chronic hepatitis B (84% males, 42% with cirrhosis)	Negative	Positive	The rate of serum HBsAg clearance was 29% in CC (major homo) compared to 13% in non-CC (hetero or minor homo) genotype carriers ($P = 0.039$)
9	2013	Seto *et al*[32]	IL28B (rs12979860, rs8099917)	203 chronic hepatitis B patients achieving spontaneous HBsAg seroclearance with 203 age- and sex-matched chronic hepatitis B patients without HBsAg seroclearance (control)	Negative	Positive	IL28B haplotype block CG was associated with HBsAg seroclearance (OR = 10.5, $P = 0.026$)
10	2013	Holmes *et al*[33]	rs12979860	96 patients (88% were Asian, 62% were HBeAg positive and 13% were METAVIR stage F3-4). The majority (84%) of patients carried the CC IL28B genotype (major homo)	Positive and negative	Negative	
11	2013	Lee *et al*[34]	rs8099917, rs12979860, rs12980275	404 spontaneously recovered patients, 313 chronic hepatitis B patients, 305 liver cirrhosis patients and 417 hepatocellular carcinoma patients	ND	Negative	

Studies are chronologically numbered. HBV: Hepatitis B virus; ND: Not determined or not described; IL: Interleukin; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen; PEG-IFN: Pegylated interferon-α.

effect of rs8099917 in *IL-28B* gene as well as rs187238 and rs1946518 in *IL-18* gene on HBV recurrence in liver transplant patients was investigated in a Chinese Han population[29]. In 140 HBV-related liver transplant recipients, the genotype of *IL-28B* gene rs8099917 was associated with aminotransferase levels. The recipients with allele G (GG + GT) had higher aminotransferase levels ($P < 0.05$). No association was found between *IL-18* gene and *IL28B* gene polymorphisms with HBV recurrence in the liver transplant recipients or the donors. The authors concluded that allele G of rs8099917 was associated with hepatitis B-related hepatocyte injury. Association analysis between SNPs in *IL-28B* gene and the progress of HBV infection in Han Chinese revealed[30] that *IL-28B* rs12979860 C/T polymorphism T allele appeared to be more prevalent in patients with HCC than in those with liver cirrhosis.

In 2013, a positive association between *IL-28B* genetic polymorphism and the outcome of CH-B[31] was reported. A hundred and one HBeAg-negative patients (92% genotype D) with compensated CH-B were followed for a median of 11 (1-17) years after a median of

23 (10-48) mo of either standard or PEG IFN-α therapy. The rs12979860 (C > T) genotype in the *IL28B* locus was assessed. During a median of 11 years of post-treatment follow-up, 21 (21%) patients cleared serum HBsAg, including 15 who developed > 10 IU/mL anti-HBs titers. Forty-eight patients (47%) had CC genotype, 42 (42%) CT and 11 (11%) TT, the allelic frequency being 68% for C allele and 32% for T allele. The rate of serum HBsAg clearance was 29% (n = 14) in CC compared to 13% (n = 7) in non-CC genotype carriers (P = 0.039). Baseline HBV DNA levels < 6 log cp/mL (OR = 11.9, 95%CI: 2.8-50.6, P = 0.001), ALT levels >136 IU/mL (OR = 6.5, 95%CI: 1.8-22.5, P = 0.003), duration of IFN (OR = 1.16, 95%CI: 1.02-1.31, P = 0.021) and genotype CC (OR = 3.9, 95%CI: 1.1-13.2, P = 0.025) independently predicted HBsAg clearance. The authors concluded that *IL28B* polymorphism is an additional predictor of off-therapy IFN-related HBsAg seroclearance in HBeAg-negative patients chronically infected by genotype D HBV. Another work published in 2012[32] revealed that HLA-DP and IL28B genetic polymorphisms were associated with spontaneous HBsAg seroclearance in chronic hepatitis B patients.

In 2013, two reports concerning *IL28B* genetic polymorphism and the therapeutic outcome with PEG-IFN or natural course of CH-B failed to show any meaningful association between both[33,34]. In contrast, the SNP upstream of *IL28B* which has the strongest genetic association with HCV recovery had an inverse influence on HBV recovery[35] in a recent Korean study. *IL28B* polymorphism correlated with active hepatitis in patients with HBeAg-negative CH-B[36]. Jilg *et al*[37] describe and summarize potent associations between *IL28B* genetic polymorphism and chronic HBV infection in their review. Table 1 summarizes the possible association between *IL28B* genetic polymorphism and the effect of IFN-α or PEG-IFN in HBV infection, or spontaneous HBsAg seroclearance.

FUTURE PERSPECTIVE

As mentioned above, there is still controversy regarding the true association between *IL28B* genetic polymorphism and chronic HBV infection. More evidence is required to obtain a final conclusion and a number of prospective studies with large cohorts of patients are needed to accomplish this purpose.

REFERENCES

1 **Ge D**, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, Heinzen EL, Qiu P, Bertelsen AH, Muir AJ, Sulkowski M, McHutchison JG, Goldstein DB. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. *Nature* 2009; **461**: 399-401 [PMID: 19684573 DOI: 10.1038/nature08309]

2 **Suppiah V**, Moldovan M, Ahlenstiel G, Berg T, Weltman M, Abate ML, Bassendine M, Spengler U, Dore GJ, Powell E, Riordan S, Sheridan D, Smedile A, Fragomeli V, Müller T, Bahlo M, Stewart GJ, Booth DR, George J. IL28B is associated with response to chronic hepatitis C interferon-alpha and ribavirin therapy. *Nat Genet* 2009; **41**: 1100-1104 [PMID: 19749758 DOI: 10.1038/ng.447]

3 **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, Mizokami M. Genome-wide association of IL28B with response to pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Nat Genet* 2009; **41**: 1105-1109 [PMID: 19749757 DOI: 10.1038/ng.449]

4 **Thomas DL**, Thio CL, Martin MP, Qi Y, Ge D, O'Huigin C, Kidd J, Kidd K, Khakoo SI, Alexander G, Goedert JJ, Kirk GD, Donfield SM, Rosen HR, Tobler LH, Busch MP, McHutchison JG, Goldstein DB, Carrington M. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. *Nature* 2009; **461**: 798-801 [PMID: 19759533 DOI: 10.1038/nature08463]

5 **Rauch A**, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, Bochud M, Battegay M, Bernasconi E, Borovicka J, Colombo S, Cerny A, Dufour JF, Furrer H, Günthard HF, Heim M, Hirschel B, Malinverni R, Moradpour D, Müllhaupt B, Witteck A, Beckmann JS, Berg T, Bergmann S, Negro F, Telenti A, Bochud PY. Genetic variation in IL28B is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology* 2010; **138**: 1338-145, 1345.e1-7 [PMID: 20060832 DOI: 10.1053/j.gastro.2009.12.056]

6 **World Health Organization**. Hepatitis B fact Sheet no. 204. Cited12 April 2012. Available from: URL: http://www.who.int/mediacentre/factsheets/fs204/en/index.html

7 **Lavanchy D**. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. *J Viral Hepat* 2004; **11**: 97-107 [PMID: 14996343]

8 **Sheppard P**, Kindsvogel W, Xu W, Henderson K, Schlutsmeyer S, Whitmore TE, Kuestner R, Garrigues U, Birks C, Roraback J, Ostrander C, Dong D, Shin J, Presnell S, Fox B, Haldeman B, Cooper E, Taft D, Gilbert T, Grant FJ, Tackett M, Krivan W, McKnight G, Clegg C, Foster D, Klucher KM. IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat Immunol* 2003; **4**: 63-68 [PMID: 12469119]

9 **Honda M**, Sakai A, Yamashita T, Nakamoto Y, Mizukoshi E, Sakai Y, Yamashita T, Nakamura M, Shirasaki T, Horimoto K, Tanaka Y, Tokunaga K, Mizokami M, Kaneko S. Hepatic ISG expression is associated with genetic variation in interleukin 28B and the outcome of IFN therapy for chronic hepatitis C. *Gastroenterology* 2010; **139**: 499-509 [PMID: 20434452 DOI: 10.1053/j.gastro.2010.04.049]

10 **Urban TJ**, Thompson AJ, Bradrick SS, Fellay J, Schuppan D, Cronin KD, Hong L, McKenzie A, Patel K, Shianna KV, McHutchison JG, Goldstein DB, Afdhal N. IL28B genotype is associated with differential expression of intrahepatic interferon-stimulated genes in patients with chronic hepatitis C. *Hepatology* 2010; **52**: 1888-1896 [PMID: 20931559 DOI: 10.1002/hep.23912]

11 **Chen L**, Borozan I, Feld J, Sun J, Tannis LL, Coltescu C, Heathcote J, Edwards AM, McGilvray ID. Hepatic gene expression discriminates responders and nonresponders in treatment of chronic hepatitis C viral infection. *Gastroenterology* 2005; **128**: 1437-1444 [PMID: 15887125]

12 **Sarasin-Filipowicz M**, Oakeley EJ, Duong FH, Christen V, Terracciano L, Filipowicz W, Heim MH. Interferon signaling and treatment outcome in chronic hepatitis C. *Proc Natl Acad Sci USA* 2008; **105**: 7034-7039 [PMID: 18467494 DOI: 10.1073/pnas.0707882105]

13 **Marukian S**, Andrus L, Sheahan TP, Jones CT, Charles ED, Ploss A, Rice CM, Dustin LB. Hepatitis C virus induces interferon-λ and interferon-stimulated genes in primary liver cultures. *Hepatology* 2011; **54**: 1913-1923 [PMID: 21800339 DOI: 10.1002/hep.24580]

14 **Robek MD**, Boyd BS, Chisari FV. Lambda interferon inhibits hepatitis B and C virus replication. *J Virol* 2005; **79**: 3851-3854

[PMID: 15731279]
15 **Shindo H**, Maekawa S, Komase K, Miura M, Kadokura M, Sueki R, Komatsu N, Shindo K, Amemiya F, Nakayama Y, Inoue T, Sakamoto M, Yamashita A, Moriishi K, Enomoto N. IL-28B (IFN-λ3) and IFN-α synergistically inhibit HCV replication. *J Viral Hepat* 2013; **20**: 281-289 [PMID: 23490373 DOI: 10.1111/j.1365-2893.2012.01649.x]
16 **Nakagawa S**, Hirata Y, Kameyama T, Tokunaga Y, Nishito Y, Hirabayashi K, Yano J, Ochiya T, Tateno C, Tanaka Y, Mizokami M, Tsukiyama-Kohara K, Inoue K, Yoshiba M, Takaoka A, Kohara M. Targeted induction of interferon-λ in humanized chimeric mouse liver abrogates hepatotropic virus infection. *PLoS One* 2013; **8**: e59611 [PMID: 23555725 DOI: 10.1371/journal.pone.0059611]
17 **Muir AJ**, Shiffman ML, Zaman A, Yoffe B, de la Torre A, Flamm S, Gordon SC, Marotta P, Vierling JM, Lopez-Talavera JC, Byrnes-Blake K, Fontana D, Freeman J, Gray T, Hausman D, Hunder NN, Lawitz E. Phase 1b study of pegylated interferon lambda 1 with or without ribavirin in patients with chronic genotype 1 hepatitis C virus infection. *Hepatology* 2010; **52**: 822-832 [PMID: 20564352 DOI: 10.1002/hep.23743]
18 **Zhang S**, Kodys K, Li K, Szabo G. Human type 2 myeloid dendritic cells produce interferon-λ and amplify interferon-α in response to hepatitis C virus infection. *Gastroenterology* 2013; **144**: 414-425.e7 [PMID: 23089201 DOI: 10.1053/gastro.2012.10.034]
19 **Yoshio S**, Kanto T, Kuroda S, Matsubara T, Higashitani K, Kakita N, Ishida H, Hiramatsu N, Nagano H, Sugiyama M, Murata K, Fukuhara T, Matsuura Y, Hayashi N, Mizokami M, Takehara T. Human blood dendritic cell antigen 3 (BDCA3)(+) dendritic cells are a potent producer of interferon-λ in response to hepatitis C virus. *Hepatology* 2013; **57**: 1705-1715 [PMID: 23213063 DOI: 10.1002/hep.26182]
20 **Martin MP**, Qi Y, Goedert JJ, Hussain SK, Kirk GD, Hoots WK, Buchbinder S, Carrington M, Thio CL. IL28B polymorphism does not determine outcomes of hepatitis B virus or HIV infection. *J Infect Dis* 2010; **202**: 1749-1753 [PMID: 20977343 DOI: 10.1086/657146]
21 **Li W**, Jiang Y, Jin Q, Shi X, Jin J, Gao Y, Pan Y, Zhang H, Jiang J, Niu J. Expression and gene polymorphisms of interleukin 28B and hepatitis B virus infection in a Chinese Han population. *Liver Int* 2011; **31**: 1118-1126 [PMID: 21745278 DOI: 10.1111/j.1478-3231.2011.02507.x]
22 **Tseng TC**, Yu ML, Liu CJ, Lin CL, Huang YW, Hsu CS, Liu CH, Kuo SF, Pan CJ, Yang SS, Su CW, Chen PJ, Chen DS, Kao JH. Effect of host and viral factors on hepatitis B e antigen-positive chronic hepatitis B patients receiving pegylated interferon-α-2a therapy. *Antivir Ther* 2011; **16**: 629-637 [PMID: 21817184 DOI: 10.3851/IMP1841]
23 **Sonneveld MJ**, Wong VW, Woltman AM, Wong GL, Cakaloglu Y, Zeuzem S, Buster EH, Uitterlinden AG, Hansen BE, Chan HL, Janssen HL. Polymorphisms near IL28B and serologic response to peginterferon in HBeAg-positive patients with chronic hepatitis B. *Gastroenterology* 2012; **142**: 513-520.e1 [PMID: 22108195 DOI: 10.1053/j.gastro.2011.11.025]
24 **Wu X**, Xin Z, Zhu X, Pan L, Li Z, Li H, Liu Y. Evaluation of susceptibility locus for response to interferon-α based therapy in chronic hepatitis B patients in Chinese. *Antiviral Res* 2012; **93**: 297-300 [PMID: 22209781 DOI: 10.1016/j.antiviral.2011.12.009]
25 **de Niet A**, Takkenberg RB, Benayed R, Riley-Gillis B, Weegink CJ, Zaaijer HL, Koot M, Jansen PL, Beld MG, Lopatin U, Reesink HW. Genetic variation in IL28B and treatment outcome in HBeAg-positive and -negative chronic hepatitis B patients treated with Peg interferon alfa-2a and adefovir. *Scand J Gastroenterol* 2012; **47**: 475-481 [PMID: 22263608 DOI: 10.3109/00365521.2011.648952]
26 **Peng LJ**, Guo JS, Zhang Z, Shi H, Wang J, Wang JY. IL28B rs12979860 polymorphism does not influence outcomes of hepatitis B virus infection. *Tissue Antigens* 2012; **79**: 302-305 [PMID: 22239156 DOI: 10.1111/j.1399-0039.2011.01835.x]
27 **Martín-Carbonero L**, Rallón NI, Benito JM, Poveda E, González-Lahoz J, Soriano V. Short communication: Does interleukin-28B single nucleotide polymorphisms influence the natural history of hepatitis B? *AIDS Res Hum Retroviruses* 2012; **28**: 1262-1264 [PMID: 22324878]
28 **Ren S**, Lu J, Du X, Huang Y, Ma L, Huo H, Chen X, Wei L. Genetic variation in IL28B is associated with the development of hepatitis B-related hepatocellular carcinoma. *Cancer Immunol Immunother* 2012; **61**: 1433-1439 [PMID: 22310928 DOI: 10.1007/s00262-012-1203-y]
29 **Li Y**, Shi Y, Chen J, Cai B, Ying B, Wang L. Association of polymorphisms in interleukin-18 and interleukin-28B with hepatitis B recurrence after liver transplantation in Chinese Han population. *Int J Immunogenet* 2012; **39**: 346-352 [PMID: 22325058 DOI: 10.1111/j.1744-313X.2012.01097.x]
30 **Chen J**, Wang L, Li Y, Cai B, Fu Y, Liao Y, Zhang J. Association analysis between SNPs in IL-28B gene and the progress of hepatitis B infection in Han Chinese. *PLoS One* 2012; **7**: e50787 [PMID: 23227209 DOI: 10.1371/journal.pone.0050787]
31 **Lampertico P**, Viganò M, Cheroni C, Facchetti F, Invernizzi F, Valveri V, Soffredini R, Abrignani S, De Francesco R, Colombo M. IL28B polymorphisms predict interferon-related hepatitis B surface antigen seroclearance in genotype D hepatitis B e antigen-negative patients with chronic hepatitis B. *Hepatology* 2013; **57**: 890-896 [PMID: 22473858 DOI: 10.1002/hep.25749]
32 **Seto WK**, Wong DK, Kopaniszen M, Proitsi P, Sham PC, Hung IF, Fung J, Lai CL, Yuen MF. HLA-DP and IL28B polymorphisms: influence of host genome on hepatitis B surface antigen seroclearance in chronic hepatitis B. *Clin Infect Dis* 2013; **56**: 1695-1703 [PMID: 23449268 DOI: 10.1093/cid/cit121]
33 **Holmes JA**, Nguyen T, Ratnam D, Heerasing NM, Tehan JV, Bonanzinga S, Dev A, Bell S, Pianko S, Chen R, Visvanathan K, Hammond R, Iser D, Rusli F, Sievert W, Desmond PV, Bowden DS, Thompson AJ. IL28B genotype is not useful for predicting treatment outcome in Asian chronic hepatitis B patients treated with pegylated interferon-α. *J Gastroenterol Hepatol* 2013; **28**: 861-866 [PMID: 23301835 DOI: 10.1111/jgh.12110]
34 **Lee DH**, Cho Y, Seo JY, Kwon JH, Cho EJ, Jang ES, Kwak MS, Cheong JY, Cho SW, Lee JH, Yu SJ, Yoon JH, Lee HS, Kim CY, Shin HD, Kim YJ. Polymorphisms near interleukin 28B gene are not associated with hepatitis B virus clearance, hepatitis B e antigen clearance and hepatocellular carcinoma occurrence. *Intervirology* 2013; **56**: 84-90 [PMID: 23343781 DOI: 10.1159/000342526]
35 **Kim SU**, Song KJ, Chang HY, Shin EC, Park JY, Kim do Y, Han KH, Chon CY, Ahn SH. Association between IL28B polymorphisms and spontaneous clearance of hepatitis B virus infection. *PLoS One* 2013; **8**: e69166 [PMID: 23874902 DOI: 10.1371/journal.pone.0069166]
36 **Lee IC**, Lin CH, Huang YH, Huo TI, Su CW, Hou MC, Huang HC, Lee KC, Chan CC, Lin MW, Lin HC, Lee SD. IL28B polymorphism correlates with active hepatitis in patients with HBeAg-negative chronic hepatitis B. *PLoS One* 2013; **8**: e58071 [PMID: 23469142 DOI: 10.1371/journal.pone.0058071]
37 **Jilg N**, Chung RT. One more piece in the interleukin 28B gene puzzle? The case of hepatitis B. *Hepatology* 2013; **57**: 870-872 [PMID: 22911469 DOI: 10.1002/hep.26026]

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