

IL-28B Genetic Analysis And HBV Disease Association Studies With Small Number Study Subjects; Should We Rely On Results?

Muhammad Sohail Afzal

Muhammad Sohail Afzal, Department of Life Sciences, School of Science, University of Management and Technology (UMT), Lahore, Pakistan

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Muhammad Sohail Afzal, Department of Life Sciences, School of Science, University of Management and Technology (UMT), Lahore, Pakistan.

Email: sohail.ncvi@gmail.com

Telephone: +92-321-5244808

Received: October 20, 2016

Revised: December 24, 2017

Accepted: December 25, 2017

Published online: December 26, 2017

ABSTRACT

Hepatitis B Virus (HBV) is one of the leading cause of cirrhosis and hepatocellular carcinoma worldwide. The virus has 10 different genotypes and has a specific geographic distribution for each genotype. Viral genotypes and certain mutations in the viral genome are associated with differential clinical features and therapeutic response. It is also evident that during HBV infection certain host genetic factors play major role in determining the outcome of infection and also impact the outcomes of antiviral therapy. IL28B plays an important role in the outcome of HBV infection and it could inhibit the viral replication. There are some functional genetic variants in IL28B gene which regulate the expression of IL28B. These genetic variants played significant role in predicting

the antiviral therapy response and disease progression. There are several case control studies across the globe which are investigating the role of these functional variants on disease progression and antiviral therapy outcomes. In current study the available data on the genetic analysis of IL28B variants and their impact on HBV disease progression or antiviral therapy response is analyzed. The results showed that most of the studies including only small number of study participants hence the low sample number impact the power of statistical analysis. It is proposed that in future the case control studies must be conducted on large scale so statistical results can be justified and will be of help in clinical settings.

Key words: IL-28B; HBV; Ethnicity; Genetic analysis; Case-control studies

© 2017 The Author(s). Published by ACT Publishing Group Ltd. All rights reserved.

Afzal MS. IL-28B Genetic Analysis And HBV Disease Association Studies With Small Number Study Subjects; Should We Rely On Results? *Journal of Gastroenterology and Hepatology Research* 2017; 6(6): 2502-2504 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/2171>

DEAR EDITOR

The major recent breakthrough in genetics and hepatology is the role of variations found in the region of interleukin-28B (IL28B), the gene coding for the IL28B protein, also known as interferon (IFN)- λ 3. The genetic variations in this region are highly predictive of pegylated INF alpha (Peg-IFN- α) and ribavirin (RBV) therapy response and viral clearance in different ethnic groups of chronic hepatitis C patients^[1]. Recently there are growing numbers of studies on investigating the role of these genetic variations in different ethnic groups and Peg-IFN- α and RBV treatment response in hepatitis B patients.

A report published by Holmes *et al* (2013) showed that IL28B genotype (rs12979860) is not a useful predicting marker for treatment outcome in Asian chronic hepatitis B patients treated with pegylated interferon- α . The study includes very small number of patients as well control subjects. Conclusion of the study based

Table 1 Summary of studies investigating IL-28B polymorphic variants association with HBV disease susceptibility, progression and Interferon ribavirin therapy response.

Year	Ethnicity	Settings		Conclusion/Association with IL-28 Polymorphism	Reference
		Patients (n)	Control (n)		
2013	Italian	101	-	Good predictor of Interferon ribavirin therapy response	3
2013	Taiwanese	115	-	Positive association with disease susceptibility	4
2013	Hong Kong	203	203	Positive association with disease susceptibility	5
2012	Chinese Han	1205	244	Positive association with disease progression	6
2012	Chinese	140	150	No association with HBV recurrence in the liver transplant recipients or the donors.	7
2012	Han Chinese	283	47	Positive association with disease susceptibility and chronicity	8
2012	Spanish	49	49	No association with disease susceptibility	9
2012	Taiwanese	133	-	No association with disease progression and chronicity	10
2012	Chinese	512	-	Positive association with Interferon ribavirin therapy response	11
2012	Chinese	651	226	No association with disease susceptibility	12
2012	Not differentiated	205	-	Positive association with Interferon ribavirin therapy response	13
2012	Netherlands	95	-	No association with HBeAg seroconversion or HBsAg clearance	14
2011	Chinese Han	406	203	Preventive effect on disease progression	15
2011	Taiwanese	115	-	No association with HBeAg seroconversion	16
2011	Italian	292	344	Positive correlation with viral infection	17
2011	Chinese	342	144	No correlation with the outcome of HBV infection	18

on 52 patients and 32 controls from Asian ethnicity; study groups were further divided into 4 different groups on ethnic basis. The study includes 8, 14, 22, 8 patients of Cambodian, Chinese, Vietnam and other ethnic background respectively. Similarly the control group from Cambodian, Chinese, Vietnam and other ethnicity includes 7, 9, 11 and 5 individuals respectively. The Caucasian and African study groups includes 7, 1 patients and 2, 2 healthy control respectively^[2]. The results showed that CC IL28B genotype was the major prevalent genotype and was present in 85% patients and 83.3% healthy individuals followed by CT genotype which was present in 15% patients and 13.9% controls. Genotype TT prevalence was 0% in cases and 2.8% in controls; the very low prevalence was may be due to very small number of investigated individuals. On the basis of these results authors concluded that IL-28B polymorphism (rs12979860) has no association with pegylated interferon therapy outcomes in HBV patients with Asian ethnic background.

The findings of other reports analyzing the role of IL-28B polymorphic variants on HBV infection susceptibility and therapy outcomes from different groups are conflicting but were based on comparatively larger number of patients and controls (Table 1)^[3-18]. A recent report by Chen *et al*^[6] investigated the IL-28B Gene polymorphism association and the Progress of Hepatitis B Infection in Han Chinese. Irrespective of results; the study includes 3 patients and a healthy group of 406, 406, 393 and 244 individuals respectively. A summary of all available studies in PubMed investigating the role of IL-28B polymorphism with respect to HBV infection is given in Table 1. The main problem of case control studies for genetic analysis of host genetic markers is the number of individuals being analyzed. The studies based on small number of samples like 1, 2, 7, 8 individuals may showed statistically false positive or false negative association. Therefore care should be taken while concluding such kind of studies. It is highly recommended that this kind of investigation must include larger study groups and should be done on larger scale.

REFERENCES

1. 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]
2. 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-a. *Journal of Gastroenterology and Hepatology* 2013; **28(5)**: 861-866. [PMID: 23301835]; [DOI: 10.1111/jgh.12110]
3. 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(3)**: 890-896. [PMID: 22473858]; [DOI: 10.1002/hep.25749]
4. 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(2)**: e58071. [PMID: 23469142]; [DOI: 10.1371/journal.pone.0058071]
5. Seto Wk, Wong DK, Kopaniszen M, Proitsi P, Sham P, Hung IF, Fung J, Lai C, Yuen M. HLA-DP and IL28B Polymorphisms: Influence of Host Genome on Hepatitis B Surface Antigen Seroclearance in Chronic Hepatitis B. *Clin Infect Dis* 2013; **56(12)**: 1695-1703. [PMID: 23449268]; [DOI: 10.1093/cid/cit121]
6. 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(12)**: e50787. [PMID: 23227209]; [DOI: 10.1371/journal.pone.0050787]
7. 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(4)**: 346-352. [PMID: 22325058]; [DOI: 10.1111/j.1744-313X.2012.01097.x]
8. 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**(9): 1433-1439. [PMID: 22310928]; [DOI: 10.1007/s00262-012-1203-y]
9. 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**(10): 1262-1264. [PMID: 22324878]; [DOI: 10.1089/AID.2011.0365]
 10. Lin CL, Tseng TC, Su TH, Liu CJ, Chen PJ, Lai MY, Chen DS, Kao JH. Host genetic variants and hepatitis B virologic features in HBeAg-negative hepatitis B carriers with long-term biochemical remission. *Hepatology International* 2012; **6**(3): 598-605. [PMID: 21779934]; [DOI: 10.1007/s12072-011-9297-4]
 11. 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**(2): 297-300. [PMID: 22209781]; [DOI: 10.1016/j.antiviral.2011.12.009]
 12. 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**(4): 302-305. [PMID: 22239156]; [DOI: 10.1111/j.1399-0039.2011.01835.x]
 13. 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 serological response to peginterferon in HBeAg-positive patients with chronic hepatitis B. *Gastroenterology* 2012; **142**(3): 513-520. [PMID: 22108195]; [DOI: 10.1053/j.gastro.2011.11.025]
 14. 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**(4): 475-481 [PMID: 22263608]; [DOI: 10.3109/00365521.2011.648952]
 15. 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**(8): 1118-1126. [PMID: 21745278]; [DOI: 10.1111/j.1478-3231.2011.02507.x]
 16. 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-a-2a therapy. *Antivir Ther* 2011; **16**(5): 629-637. [PMID: 21817184]; [DOI: 10.3851/IMP1841]
 17. Fabris C, Falletti E, Cussigh A, Bitetto D, Fontanini E, Bignulin S, Cmet S, Fornasiere E, Fumolo E, Fangazio S, Cerutti A, Minisini R, Pirisi M, Toniutto P. IL-28B rs12979860 C/T allele distribution in patients with liver cirrhosis: role in the course of chronic viral hepatitis and the development of HCC. *J Hepatol* 2011; **54**(4): 716-722. [PMID: 21146242]; [DOI: 10.1016/j.jhep.2010.07.019]
 18. Jiao XL, Gao YT, Jing L, Liu T, Shi WX, Guo H, Yang B, DU Z. Studies on the relationship between polymorphism of IL-28B rs8099917 and the outcome of HBV infection. *Zhonghua Liu Xing Bing Xue Za Zhi* 2011; **32**(11): 1143-1147. [PMID: 22336553]