HEPATITIS B VIRUS (HBV) GENOTYPE AND ITS CORRELATION WITH HEPATOCELLULAR CARCINOMA

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ABSTRACT

Hepatitis B is a viral disease caused by Hepatitis B Virus (HBV), which could cause both acute and chronic infection. HBV infection have been considered as the most common high risk factor that cause cirrhosis and subsequent development of Hepatocellular (HCC) worldwide.

Even though Hepatitis B vaccine was found to be generally safe for two decades, however, HBV infection continues to be a major public health worldwide with the death raising from 600.000 to 1 million cases. Many risk factors, including HBV genotypes, have been proved to be associated to the chronic development and, then development of HCC.

Current review was carried out to summarize the properties and prevalence of HBV genotypes, based on Vietnamese population, in order to highlight characteristic of HBV infection, simultaneously analyzed the correlation between HBV genotypes and other high risk factor related to HCC development.

Keywords: *Hepatitis B; HBV, genotype; Vietnamese population.*

1. Introduction

Hepatitis B is a viral disease caused by Hepatitis B virus (HBV) infection, leading cause of cirrhosis and high risk of developing hepatocellular carcinoma (HCC) worldwide.

Although the safety and effectiveness of vaccines prevented HBV has been proven through more than two decades, but HBV infection continues to grow globally with approximately 600,000 to 1 million deaths each year.

There are many rick factors are related to the progression of the HBV infection disease into a chronic, thereby transferred to HCC, including HBV genotype factor.

This review will summarize some the characteristics of HBV genotypes, in which rate data are collected mostly based on the published using samples of Vietnam population, in order to highlight some special characteristics about this kind of infectious disease. Furthermore, the simultaneous analysis of several related properties between HBV genotypes with other factors will be taken into account in the risk of HCC.

2. Genotype characteristics and rates of HBV genotype

Based on the degree of similarity in the nucleotide sequence, HBV is divided into 8 different genotypes (noted from A to H) with a difference in 8% of the entire HBV genome (Norder *et al*, 1998; Okamoto *et al*, 1988). The distribution of HBV genotypes varies depended by geography (Okamoto *et al*, 1988; Norder *et al*, 1993). Worldwide, in recent years, there have been many published on HBV genotype and its correlation with the severity of the HBV infection disease,

especially the transition to HCC (Oyagbemi *et al.*, 2010; Neuveut *et al.*, 2010; Sinn *et al*., 2015)

As we just mentioned above, HBV genotype distribution varied by geography; in which genotype B and C are common in Southeast Asia, Japan and the Pacific region, and the prevalence of genotype B generally is higher than C (Okamoto *et al*, 1988; Norder *et al*, 1993; Norio, Hiromitsu 2005; Dong Thi Hoai An, Cao Minh Nga, 2003; Do Thi Thuy Duong, Le Huyen Ai Thuy, 2010; Kao Jia-Horng, 2011).

In HT Tran *et al* (2003) publication, 295 blood samples collected from liver disease patients in HoChiMinh city were analyzed. The authors noted in 234/295 cases of HBV infection which accounted for 43 and 57% of each genotype B and C, respectively. Thus, the prevalence between genotype B/C is approximately 1/1; and no one other than above genotype mentioned was recorded.

Another study was carried out in the period from August/2006 to May/2006 at Medic Medical Center (Ho Tan Dat *et al*), the authors applied PCR sequencing method of 122 chronic HBV infection cases treated by Lamivudine and consequently recorded only 2 genotypes B and C, in which, the genotype B was 76 infected cases (counting at 62.3%) and genotype C was 46 cases (counting at 37.7%). So, prevalence between genotype B/C is approximately 2/1.

Another study of Long H. Nguyen *et al* (2009) performed on American patients with chronic HBV infection grouped in Vietnamese or Chinese origin living in Northern California from June/2005 to June/02008. The authors also noted a high rate difference between the two groups, in which, Chinese patients were infected by genotype B accounted for 49/89 cases (counting at 55%), genotype C accounted for 38/89 cases (counting at 43%) and two case infected by genotype D (counting at 2%). Meanwhile, Vietnamese patients, this percentage was distributed among the proportion to genotype B accounted 335/478 cases (counting at 74%), genotype C accounted 120/478 cases (counting at 24%), genotype A occupied only one case and genotype D accounted 2/478 cases (counting at approximately 1%). Thus, HBV genotypes infect mainly with ethnic Vietnamese community is genotype B and C, in which, the ratio between B/C was recorded at around 3/1.

In another publication by Mai Anh Tuan Dang *et al* (2011), HBV genotyping survey was performed by PCR-sequencing on a sample size of 894 patients. The authors noted with 3 genotype B, C and D, but D genotype occupied only one case accounted for 0.11% of the sample. The remaining were infected by 678 samples of genotype B (counting at 75.84%) and genotype C with 215 cases (counting at 24.05%), means the ratio of genotype B/C is about 3/1.

The study of TB Phung *et al* (2010) also found that of 87 samples from patients infected by HBV in Hanoi, genotype B accounted for 67/87 samples (counting at 77%) and genotype C accounted for 19/87 samples (counting at 22%), *i.e* the ratio of genotype B/C at about 3/1.

In some other studies using real-time PCR for genotyping, the authors noted in 66 cases acquired HBV DNA positive in Dong Thap Hospital, genotype B accounted for 39 cases (counting at 59.1%), genotype C accounted for 21 cases (counting at 31.8%) and 6 cases (counting at 9.1%) co-infection by two genotypes B and C; So, prevalence between genotype B/C at about 2/1 (Lao Duc Thuan *et al*, 2014); In 100 cases of HBV DNA positive in Daklak Province Hospital, 63 samples infected by B genotypes and 21 samples infected by C genotypes, i.e prevalence between genotype B/C approximately 3/1, also 16 samples simultaneously infected by both genotype B and C (Do Thi Thuy Duong, Le Huyen Ai Thuy, 2010); In 147 cases of HBV DNA positive in Tay Ninh Hospital, genotype B accounted for 115 cases (counting at 78.2%), genotype C

accounted for 26 cases (counting at 17.7%) and 6 cases (counting at 4.1%) co-infected by both genotype B and C. Thus, the prevalence between genotype B/C is approximately 4/1 (Truong Kim Phuong *et al*, 2013).

The publication in 2011 by Nguyen CH *et al* also showed that the prevalence of HBV infection in 113 patients in the area of Hai Phong city was genotype B accounted for 80.5%, while genotype C accounted for nearly 20%, i.e prevalence between genotype B/C at around 4/1.

Dunford L *et al* (2012) showed that of the 185 samples infected by HBV that collected from Ha Noi, Hai Phong, Da Nang, Khanh Hoa and Can Tho, genotype B represented approximately 85%, meanwhile genotype C accounting for approximately 15%. Thus, infection rates of genotype B/C are larger at around 5/1.

Thus, we can summarize that HBV genotyped on the Vietnam communities similar to the previous comments about the infected genotype, that genotype B and C are two infected majority in Asian region; genotype B proportion is always much higher rate, about 3 times higher than genotype C and trend of genotype B infection is increasing from 2/1 to 3/1, 4/1 and 5/1; This also may be a special characteristic of HBV Vietnames infected patients.

3. Correlation between genotype and other factors, the risk of leading to HCC

HBV genotype is considered to be related to the status of the disease latent (through the evaluation of HBcAg and HBeAg concentration); the pathogenesis of the liver; the HBV escaping from the immune system, the response to the treatment and anti-viral medications, which involves the risk transferred to HCC (Norio, Hiromitsu, 2005; Lindh *et al*, 1999; Thakur *et al*, 2002; Erhardt *et al*, 2000; Kao *et al*, 2000; Thakur *et al*, 2005; Janssen *et al*, 2004; Kao *et al*, 2002; Kumar *et al*, 2005).

Considering the relationship between genotype and HBV DNA levels, one of the criteria for assessing the status of the viral infection, the severity of the disease and also the risk of HCC transfer; then in the different studies showed conflicting results.

A study has shown that the infected patients with genotype C, HBV DNA levels in blood higher than genotype B (Thakur *et al*, 2005). In another study on 694 patients with stage III HBV applied Adefovir dipivoxil therapy, it showed that those infected with genotype C (in the case of only the HBeAg positive), higher HBV DNA levels compared to other genotypes. In contract, patients with HBeAg negative, HBV genotype D patients had higher DNA concentration than the remaining genotypes (Norio, Hiromitsu 2005).

Among the factors that are considered to have affected to disease progression, *i.e* increasing or reducing the risk of HCC transfers; that is the assessment of the response to the treatment using interferon, slowly response to interferon-α therapy (Lin *et al*, 2011). HBV genotype C usually appears the higher frequency of basal core promoter mutations compared to genotype B, deletion of *preS* region occurs frequently, also often comes with higher viral load (Lin *et al*, 2011).

In the published by Yu MW *et al* (2005), the authors reported on 4841 Taiwan male patients, genotype C viral load is higher than genotype B, so the risk of HCC is higher 26 times more than the other genotypes. However, some of the retrospective studies (Sumi *et al*, 2003; Chu *et al*, 2002), and especially in study of Chu JC *et al* (2002), such observation have not proven, means the correlation between genotype and viral load is still investigated.

Analysis of the research results of Truong Kim Phuong *et al* (2013), it showed that viral load in patients infected by genotype C [median viral load of genotype C carriers is

12,800 (227.9-216,000) UI/mL) and B & C co-infection is 42.900 (1815-6,430,000) UI/mL] which was higher than genotype B carriers [2024 (340-604,000) IU/mL]. Infected C and B & C co-infected patients have a higher viral load than infected genotype B, although this difference was not reached statistical significance (p = 0.84) (Truong Kim Phuong *et al*, 2013). Patients infected by genotype C or B & C have ALT index higher than genotype B infection [median of ALT levels in genotype B carriers was 25 (19-43) IU/mL; genotype C carriers was 33.5 (26.25-64.25) IU/mL, and with both genotypes B & C were 43 (21.5-64.5) IU/mL]. This difference was closed to the statistically significant (p = 0.075) (Truong Kim Phuong *et al*, 2013).

Another study was conducted on 2762 Taiwan patients; despite the viral load factor was not mentioned in this research, but the authors also recognized genotype C liver dysfunction are so severity than genotype B as well as genotype C is so easy to take progress of cirrhosis, leading to HCC higher compared to genotype B (Yang *et al*, 2008).

The relationship between HBV genotype and HCC has been noted in other studies through a number of other evaluation criteria, in which, genotype B is frequently associated with the development of HCC in younger patients; other studies showed that genotype C is frequently associated with HCC and HCC recurrence rates higher after surgical resection of liver cancer cells compared with genotype B (Yang *et al*, 2008; Kao *et al*, 2000; Ding *et al*, 2001; Sakugawa *et al*, 2002; Ni *et al*, 2004; Yin *et al*, 2008). The hypothesis was put forward to explaining this is genotype B needs a shorter time to reproduce at a high level, so that consequently infected properties are less than (Chu *et al*, 2003).

Some studies also showed that HBV genotype B HBeAg excreted higher than genotype C, in other words, genotype C is thought to delay the blood circulation and HbeAg increased risk HCC higher to other genotypes (Thakur *et al*, 2005; Chan *et al*, 2002; Ren *et al*, 2010; Chan *et al*, 2003). Kao JH *et al* (2002) reported on 272 Taiwan chronic HBV patients, in which, genotype C had higher HBeAg positive compared to genotype B.

The level of circulating HBeAg was recorded from 146 Taiwan patients in 52 months indicating that genotype C delays blood circulating HBeAg higher than genotype B (47% of genotype C compared to 27% of genotype B, p < 0.025). The level of genotype B and C excretion is estimated to 15.5 and 7.9%, respectively (Kao *et al*, 2004).

Truong Kim Phuong *et al* (2013) also found that the difference among HBeAg-negative carriers genotype B, C and B & C co-infection was 68.7%, 50% and 50%, respectively, but this difference is still not clear (p > 0.05).

Among the factors that may also affect to the severity of HBV infected disease, meaning that increases or decreases the risk of HCC transfer; that is the assessment of response to the treatment of nucleoside (NUCs) drugs. Several publications showed that infected genotype B patients easily developed Lamivudine resistant mutations than other genotypes. Chien RN *et al* (2003) confirmed that the response to Lamivudine of genotype B infected patients is higher than genotype C. However, two other studies carried out in Hong Kong gave the conflicting results (Yuen *et al*, 2003; Chan *et al*, 2003).

Another publication carried out on Spain community, Buti M *et al* (2002) and other studies have shown no difference between genotypes in response to Adefovir (Westland *et al*, 2003), Entecavir (Lurie *et al*, 2005) and Telbivudine (Hou *et al*, 2008) treatments.

A study of a large of patients was published in 2008 by Wiegand J *et al* showed absolutely no correlation between genotype

and response to NUCs drug resistance; Also the research of Raimondi S *et al* (2010) confirmed the independence between genotype and response to NUCs drug resistance. However, in the study of Hsieh TH *et al* (2009), it showed that genotype B correlated to the development of lamivudine resistance within the first 12 moths of treatment (compared to genotype C) (odds ratio – OR between the probability of resistance/non-resistance is 8.27, p = 0.004). Study of Tan YW *et al* (2012) also showed that most mutations occurred YMDD resistance in patients infected by genotype C or more dual infected by both B & C or C & D genotypes, and even some cases can not determine the infected genotypes in a mixture of infectious virus. However, this correlation is not statistically significant (χ^2 = 2,413; p = 0,878).

Publication of Ho Tan Dat *et al* that conducted from August/2004 to May/2006 on 122 patients at Medic Medical Center, Ho Chi Minh city, who noted Lamivudine-resistant mutations in genotype B (counting at 64.5%) and genotype C (counting at 63%) is nearly equal. Truong Kim Phuong *et al* (2013) also showed that the rate of Lamivudine and Adefovir resistances is no difference among the infected genotypes (p = 0.32 and p = 0.143, respectively).

In general, the issue of the influence of HBV genotype for the resistance to the NUCs drug should be studied long and in a larger number of patients as well as needs to conduct a special monitoring during treatment time to clarify the risk of this relationship with HBV infection disease, means of the transfer to HCC disease.

REFERENCES

Buti, M., Cotrina, M., Valdes, A., Jardi, R., Rodriguez-Frias, F., Esteban, R. (2002). Is hepatitis B virus subtype testing useful in predicting virological response and resistance to lamivudine?, *J. Hepatol*., 36, 445–446.

Chan, H. L., Tsang, S. W., Wong, M. L., Tse, C. H., Leung, N. W., Chan, F. K., Sung, J. J. (2002). Genotype B hepatitis B virus is associated with severe icteric flare-up of chronic hepatitis B virus infection in Hong Kong, *Am J Gastroenterol*., 97, 2629-2633.

Chan, H. L.-Y., Wong, M. L., Hui, A. Y., Hung, L. C.-T., Chan, F. K.-L., & Sung, J. J.-Y. (2003). Hepatitis B Virus Genotype C Takes a More Aggressive Disease Course Than Hepatitis B Virus Genotype B in Hepatitis B e Antigen-Positive Patients, *Journal of Clinical Microbiology*, 41(3), 1277–1279.

Chan, H. L.-Y., Wong, M.-L., Hui, A. Y., Chim, A. M.-L., Tse, A. M.-L., Hung, L. C.-T.,… Sung, J. J.-Y. (2003). Hepatitis B virus genotype has no impact on hepatitis B e antigen seroconversion after lamivudine treatment, *World Journal of Gastroenterology : WJG*, 9(12), 2695–2697.

Chien, R. N., Yeh, C. T., Tsai, S. L., Chu, C. M., Liaw, Y. F. (2003). Determinants for sustained HBeAg response to lamivudine therapy, *Hepatology*, 38, 1267–1273.

Chu, C. J., Hussain, M., Lok, A. S. (2002). Hepatitis B virus geneotype B is associated with earlier HBeAg seroconversion compared with hepatitis B virus geneotype C, *Hepatology*, 122, 1756-1762.

Chu, C. J., Keeffe, E. B., Han, S. H., Perrillo, R. P., Min, A. D., Soldevila-Pico, C. (2003). Prevalence of HBV precore/core promoter variants in the United States, *Hepatology*. 38, 619-628.

Ding, X., Mizokami, M., Yao, G., Xu, B., Orito, E., Ueda, R. (2001). Hepatitis B virus genotype distribution among chronic hepatitis B virus carriers in Shanghai Chin, *Intervirology*, 44, 43-47.

Do Thi Thuy Duong and Le Huyen Ai Thuy. (2010). Application of Real-time PCR in genotyping HBV at Daklak, *Journal of Science*, 1(19)-2011, 118-123 (in Vietnamese).

Dong Thi Hoai An, Cao Minh Nga. (2003). Genotyping Hepatitis B virus by Multiplex PCR in chronic HBV infected patients, *From Molecular Science to Life and Health Care*, 17-25 (in Vietnamese).

Dunford, L., Carr, M. J., Dean, J., Nguyen, L. T., Ta Thi, T. H., Nguyen, B. T., … Thi, L. A. N. (2012). A Multicentre Molecular Analysis of Hepatitis B and Blood-Borne Virus Coinfections in Viet Nam, *PLoS ONE*, 7(6), e39027.

Erhardt, A., Reineke, U., Blondin, D., Gerlich, W. H., Adams, O., Heintges, T., Niederau, C., Häussinger, D. (2000). Mutation of the core promoter and response to interferon in chronic replicative hepatitis B, *Hepatology.*, 31:716-725.

Ho Tan Dat, Pham Thi Thu Thuy, Nguyen Bao Toan, Nguyen Thi Kieu Oanh, Nguyen Thanh Tong. Medic Medical Center, HoChiMinh city. Application of Sequencing to genotyping and NUCs drug resistant mutations of HBV. Quote from http://www.drthuthuy.com/reseach/HBVGenotype.html (in Vietnamese).

Hou, J, Yin, Y. K., Xu, D., Tan, D., Niu, J., Zhou, X., Wang, Y., Zhu, L., He, Y., Ren, H., Wan, M., Chen, C., Wu, S., Chen, Y., Xu, J., Wang, Q., Wei, L., Chao, G., Constance, B. F., Harb, G., Brown, N. A., Jia, J. (2008). Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: results at 1 year of a randomized, double-blind trial, *Hepatology*, 47, 447–454.

Hsieh, T. H., Tseng, T. C., Liu, C. J., Lai, M. Y., Chen, P. J., Hsieh, H. L., Chen, D. S., Kao, J. H. (2009). Hepatitis B virus genotype B has an earlier emergence of lamivudine resistance than genotype C, *Antivir. Ther*., 14, 1157–1163.

Janssen, H. L., Flink, H. J., Zonneveld, M. .V., Niesters, H. G., Man, R. A. D., Schalm, S. W. (2004). HBeAg seroconversion in chronic HBV patients treated with pegylated interferon alfa-2b alone or in combination with lamivudine: the role of HBV geneotype, *Hepatology*., 40, 660A.

Kao Jia-Horng. (2011). Molecular Epidemiology of Hepatitis B virus, *Korean J Intern Med*., 26**,** 255-261.

Kao, J. H., Chen, P. J., Lai, M. Y., Chen, D. S. (2000). Hepatitis B geneotypes correlate with clinical outcomes in patients with chronic hepatitis B. *Gastroenterology*, 118, 554-559.

Kao, J. H., Chen, P. J., Lai, M. Y., Chen, D. S. (2004). Hepatitis B virus genotypes and spontaneous hepatitis B e antigen seroconversion in Taiwanese hepatitis B carriers, *J. Med. Virol*., 72, 363–369.

Kao, J. H., Liu, C. J., Chen, D. S. (2002). Hepatitis B viral geneotypes and lamivudine resistanc, *J Hepatol*., 36, 303-304.

Kao, J. H., Wu, N. H., Chen, P. J., Lai, M. Y., Chen, D. S. (2000). Hepatitis B genotype and the response to interferon therapy, *J Hepatol*., 33, 998-1002

Kao, J.-H., Chen, P.-J., Lai, M.-Y., & Chen, D.-S. (2002). Genotypes and Clinical Phenotypes of Hepatitis B Virus in Patients with Chronic Hepatitis B Virus Infection, *Journal of Clinical Microbiology*, 40(4), 1207–1209.

Kumar, A., Kumar, S. I., Pandey, R., Naik, S., Aggarwal, R. (2005). Hepatitis B virus geneotype A is more often associated with severe liver disease in northern India than is geneotype, *Indian J Gastroenterol*., 24, 19-22.

Lao Duc Thuan, Mai Ngoc Lanh, Le Thi Phuong, Phan Van Be Bay, Ho Thi Thanh Thuy, Truong Kim Phuong, Le Huyen Ai Thuy. (2014). Application of Real-time PCR in genotyping, viral load identifying, and characterizing NUCs drug resistant mutations at Dong Thap Hospital, *Journal of Science*, 6(39), 67-75 (in Vietnamese).

Lin, C. L., Kao, J. H. (2011). The clinical implications of hepatitis B virus genotype: Recent advances, *Journal of Gastroenterology and Hepatology*, 26Suppl 1, 123–130.

Lindh, M., Hannoun, C., Dhillon, A. P., Norkrans, G., Horal, P. (1999). Core promoter mutations and geneotypes in relation to viral replication and liver damage in East Asian hepatitis B virus carriers, *J Infect Dis.,* 179**,** 775-782.

Lurie, Y., Manns, M. P., Gish, R. G. (2005). The efficacy of entecavir is similar regardless of disease-related baseline subgroups in treatment of nucleoside-naive, HBeAg (+) and HBeAg (-) patients with chronic hepatitis B, *J. Hepatol.,* 42 (Suppl. 2), 184.

Neuveut, C., Wei, Y., Buendia, M. A. (2010). Mechanisms of HBV-related hepatocarcinogenesis. *J Hepatol*., 52(4), 594-604.

Nguyen, C. H., Ishizaki, A., Chung, P. T., Hoang, H. T., Nguyen, T. V., Tanimoto, T., Lihana, R., Matsushita, K., Bi, X., Pham, T. V., Ichimura, H. (2011). Prevalence of HBV infection among different HIV-risk groups in Hai Phong, Vietnam, *J Med Virol*., 83(3), 399-404.

Nguyen, L. H., Ha, N. B., Vutien, P., Ha, N. B., Garcia, R. T., Trinh, H. N., Nguyen, M. H. (2009). Prevalence of hepatitis B virus genotype B in Vietnamese patients with chronic hepatitis B. *Hepatology International*, 3(3), 461–467.

Ni, Y. H., Chang, M. H., Wang, K. J., Hsu, H. Y., Chen, H. L., Kao, J. H., Yeh, S. H., Jeng, Y. M., Tsai, K. S., Chen, D. S. (2004). Clinical relevance of hepatitis B virus genotype in children with chronic infection and hepatocellular carcinoma, *Gastroenterology*, 127, 1733–1738.

Norder, H., Courouce, A. M., Magnius, L. O. (1998). Complete genome, phylogenetic relatedness and structural proteins of six strains of the hepatitis B virus, four of which represent two new genotypes, *Virology*, 198(4), 89-503.

Norder, H., Hammas, B., Lee, S. D., Bele, C., Courouce, A. M., Mushawar, I. K, Bile, K., Magnius, L. O. (1993). Genetic relatedness of hepatitis B viral strains of diverse geographical origin and natural variation in the primary structure of the surface gene, *J. Gen .Virol*., 74**,** 1341-1348.

Norio, A. and Hiromitsu, K. (2005). Influence of hepatitis B virus geneotypes on the response to antiviral therapies, *Journal of Antimicrobial Chemotherapy*, 55**,** 139–142.

Okamoto, H., Tsuda, F., Sakagawa, H., Sastrosoewignjo, R. I., Imai, M., Miyakawa, Y. (1988). Typing hepatitis B virus by homology in nucleotide sequence comparison of surface antigen subtypes, *J. Gen .Virol*., 69, 2575-2583.

Oyagbemi, A. A., Azeez, O. I., Saba A. B. (2010). Hepatocellular carcinoma and the underlying mechanisms. *Afr Health Sci*., 10(1), 93-98.

Phung, T. B., Alestig, E., Nguyen, T. L., Hannoun, C., Lindh, M. (2010). Genotype X/C recombinant (putative genotype I) of hepatitis B virus is rare in Hanoi, Vietnam-genotypes B4 and C1 predominate. *J Med Virol*., 82(8), 1327-1333.

Raimondi, S., Maisonneuve, P., Bruno, S., Mondelli, M. U. (2010). Is response to antiviral treatment influenced by hepatitis B virus genotype?, *J.Hepatol*., 52, 441–449.

Ren, X., Xu, Z., Liu, Y., Li, X., Bai, S., Ding, N., … Xu, D. (2010). Hepatitis B virus genotype and basal core promoter/precore mutations are associated with hepatitis B-related acute-on-chronic liver failure without pre-existing liver cirrhosis, *Journal of Viral Hepatitis*, 17(12), 887–895.

Sakugawa, H., Nakasone, H., Nakayoshi, T., Orito, E., Mizokami, M., Yamashiro, T. (2002). Preponderance ofhepatitis B virus geneotype B contributes to a better prognosis of chronic HBV infection in Okinawa, Japan, *J Med Virol*., 67, 484-489.

Shiina, S., Fujino, H., Uta, Y., Tagawa, K., Unuma, T., Yoneyama, M. (1991). Relationship of HBeAg subtypes with HBeAg/anti-HBe status and chronic liver disease Part I: Analysis of 1744 HBeAg carriers, *Am J Gastroenterol*., 86, 866-871.

Sinn, D. H., Lee, J., Goo, J., Kim, K., Gwak, G. Y., Paik, Y. H., Choi, M. S., Lee, J. H., Koh, K. C., Yoo, B. C., Paik, S. W. (2015). Hepatocellular carcinoma risk in chronic hepatitis B virus-infected compensated cirrhosis patients with low viral load. *Hepatology*., 62(3), 694-701.

Sumi, H., Yokosuka, O., Seki, N., Arai, M., Imazeki, F., Kurihara, T. (2003). Influence of hepatitis B virus geneotypes on the progression of chronic type B liver disease, *Hepatology*, 7, 19-26.

Thakur, V., Guptan, R. C., Kazim, S. N., Malhotra, V., Sarin, S. K. (2002). Profile, spectrum and significance of HBV genotype in chronic liver disease patients in the Indian subcontinent, *J Gastroenterol Hepatol*., 17, 165-170.

Thakur, V., Sarin, S. K., Rehman, S., Guptan, R. C., Kazim, S. N., Kumar, S. (2005). Role of HBV genotype in predicting response to lamivudine therapy in patients with chronic hepatitis B, *Indian J Gastroenterol*., 24, 12-1.

Tran, H. T., Ushijima, H., Quang, V. X., Phuong, N., Li, T. C., Hayashi, S., Xuan Lien, T., Sata, T., Abe, K. (2003). Prevalence of hepatitis virus types B through E and genotypic distribution of HBV and HCV in Ho Chi Minh City, Vietnam, *Hepatol Res*., 26(4), 275-280.

Truong Kim Phuong, Lao Duc Thuan, Ho Thi Thanh Thuy, Lieu Chi Hung, Le Huyen Ai Thuy. (2013). Application of Real-time PCR in genotyping, viral load identifying, and characterizing NUCs drug resistant mutations at Tay Ninh Hospital, *Proceedings of National Conference in Biotechnology, the South Viet Nam*, 176 (in Vietnamese).

Westland, C., Delaney, W. 4th, Yang, H., Chen, S. S., Marcellin, P., Hadziyannis, S., Gish, R., Fry, J., Brosgart, C., Gibbs, C., Miller, M., Xiong, S. (2003). Hepatitis B virus genotypes and virologic response in 694 patients in phase III studies of adefovir dipivoxil, *Gastroenterology*, 125, 107–116.

Wiegand, J., Hasenclever, D., Tillmann, H. L. (2008). Should treatment of hepatitis B depend on hepatitis B virus genotypes? A hypothesis generated from an explorative analysis of published evidence, *Antivir. Ther*., 13, 211–220.

Yang, H. I., Yeh, S. H., Chen, P. J., Iloeje, U. H., Jen, C. L., Su, J., Wang, L. Y., Lu, S. N., You, S. L., Chen, D. S., Liaw, Y. F., Chen, C. J.; REVEAL-HBV Study Group. (2008). Associations between hepatitis B virus genotype and mutants and the risk of hepatocellular carcinoma, *J. Natl. Cancer Inst*., 100, 1134–1143.

Yin, J., Zhang, H., Li, C., Gao, C., He, Y., Zhai, Y., Zhang, P., Xu, L., Tan, X., Chen, J., Cheng, S., Schaefer, S., Cao, G. (2008). Role of hepatitis B virus genotype mixture, subgenotypes C2 and B2 on hepatocellular carcinoma: compared with chronic hepatitis B and asymptomatic carrier state in the same area, *Carcinogenesis*, 29, 1685–1691.

Yu, M. W., Yeh, S. H., Chen, P. J., Liaw, Y. F., Lin, C. L., Liu, C. J., Shih, W. L., Kao, J. H., Chen, D. S., Chen, C. J. (2005). Hepatitis B virus genotype and DNA level and hepatocellular carcinoma: a prospective study in men, *J. Natl. Cancer Inst*., 97, 265–72.

Yuen, M. F., Wong, D. K., Sablon, E., Yuan, H. J., Sum, S. M., Hui, C. K., Chan, A. O., Wang, B. C., Lai, C. L. (2003). Hepatitis B virus genotypes B and C do not affect the antiviral response to Lamivudine, *Antivir. Ther*., 8, 531–534.