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Human leukocyte antigen class I and class II genes polymorphisms might be associated with interferon α therapy efficiency of chronic hepatitis B

Xilin Zhu[a,1], Te Du[a,1], Xiaopan Wu[a,1], Xinhui Guo[b], Nifang Niu[a], Liping Pan[a], Zhenhui Xin[a], Li Wang[c], Zhuo Li[b], Hui Li[c,**], Ying Liu[a,*]

[a] National Laboratory of Medical Molecular Biology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, 5 Dongdan 3 Tiao, Beijing 100005, PR China
[b] Department of Infectious Disease, Affiliated Youan Hospital, Capital University of Medical Sciences, PR China
[c] Department of Epidemiology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, School of Basic Medicine, Peking Union Medical College, 5 Dongdan 3 Tiao, Beijing 100005, PR China

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ABSTRACT

Certain host genetic polymorphisms in human leukocyte antigen (HLA) genes are reported to be associated with response to interferon α (IFNα) therapy. Two hundred and eighteen IFNα treatment-naïve chronic hepatitis B (CHB) patients were enrolled in the present study. HLA-A, B, C and DQA1, DQB1, DRB1 gene alleles were detected by polymerase chain reaction-sequencing based typing (PCR-SBT) and PCR-sequence specific primer (PCR-SSP), respectively. Frequencies of HLA-DQB1*0303 and DRB1*08 in response group were clearly lower than those in nonresponse group ($P = 0.019$, OR = 1.81, 95%CI = 1.07–3.15; $P = 0.031$, OR = 2.43, 95%CI = 1.02–5.98, respectively). Frequencies of haplotype *1101-*4601-*0102 (HLA-A, B, C) and haplotype *0302-*0303-*09 (HLA-DQA1, DQB1, DRB1) were clearly lower than those in nonresponse group ($P = 0.009$, OR = 4.84, 95%CI = 1.29–19.48; $P = 0.031$, OR = 1.94, 95%CI = 1.01–3.73, respectively). These results suggest that patients with HLA-DQB1*0303 or DRB1*08 alleles, and haplotype *1101-*4601-*0102 (HLA-A, B, C) or haplotype *0302-*0303-*09 (HLA-DQA1, DQB1, DRB1), might be less responsive to IFNα treatment.

1. Introduction

Hepatitis B virus (HBV) is the most common cause of acute and chronic liver diseases worldwide. HBV infection results in 500 thousands to 1.2 million deaths per year caused by chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (Rehermann and Nascimbeni, 2005). Interferon α (IFNα) has been one of the first line drugs for hepatitis B due to its antiviral and immunomodulatory activities since its advent (Ormeci, 2003); however, responses to IFNα vary greatly, and only 25–50% individuals respond to IFNα after 4–6 months of treatment (Papatheodoridis and Hadziyannis, 2004). Individually tailored therapy is the ultimate goal for the therapy of HBV, which will be built upon the reorganization of factors affecting efficacy and side effects of anti-HBV drugs. Subjects with high alanine aminotransferase (ALT) level, active liver disease, and low HBV DNA level better respond to therapy (Saracco and Rizzetto, 1997). The evidence in support of genetic factors arises from several studies in Chinese population (Chu et al., 2005; Han et al., 2005; King et al., 2002; Wu et al., 2009). Moreover, a long term efficacy research of IFNα demonstrated that Asian patients respond to IFN worse than North Americans and Europeans (Lok et al., 2001).

Candidate genes of pharmacogenetic studies of IFNα in therapy of chronic hepatitis B patients have been focused on human leukocyte antigen (HLA) class II genes and interferon pathway genes. In 2002, King et al. identified an intron single nucleotide polymorphism (SNP) in eIF-2α as a greater marker for IFN response than HBV DNA level (King et al., 2002). In 2009, we studied 10 single nucleotide polymorphisms in IFN signaling pathway genes and found that the frequency of a G-T-G-A 2′,5′-oligoadenylate synthetase (OAS) haplotype was significantly higher in the non-response group than that in the response group (Wu et al., 2009).

The HLA complex located on the short arm of chromosome 6 that include HLA-A, -B, -C, and -D. The HLA-A, -B, and -C loci code for class I molecules. The HLA-D region consists of three primary subregions designated DP, DQ, and DR, and these loci code for class II molecules. Both class I and class II molecules are extremely important in immunologic processes (Lander et al., 2001). HLA class I molecules, which are expressed in most somatic nucleated cells, are largely responsible for the presentation of pathogen-derived

* Corresponding author. Tel.: +86 10 65296419; fax: +86 10 65296419.
** Corresponding author.
E-mail addresses: wuxiaopan1984@tom.com (X. Wu), lihui99360@sohu.com (H. Li), liuyingpumc@yahoo.com (Y. Liu).
[1] These authors contributed equally to this work.

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peptides from the cytosol to CD8-positive cytotoxic T-lymphocytes (CTLs), and are also target ligands for killer cell immunoglobulin-like receptors (KIRs) (Klein and Sato, 2000). HLA class II molecules, however, express on the surface of antigen presenting cells and target cells, and bind antigen peptide (including viral peptide), which can be recognized by $CD4^+$ T cell and produce immunity reaction and stimulate production of cytokine to modulate $CD8^+$ cytotoxic T cell (CTL) and promote antibody occurrence (Cao et al., 2002). HLA has been the target gene of many pharmacogenetic studies, as reviewed by Becquemont (2010). HBV is cleared through CTL killing infected cells and preventing other cells from infection. Vigorous HLA restricted $CD4^+$ T cell responses towards the hepatitis B core antigen (HBcAg) result in acute HBV infections, and in chronic hepatitis patients weak or no responses are observed (Urbani et al., 2005).

Therefore, understanding the role of host genetic variability in the antiviral therapy is helpful for creation of genetically individualized treatment. In the present study, nested case control study was applied to perform the association study between HLA-A, B, C, DQA1, DQB1, DRB1 genes and response to IFNα treatment.

2. Materials and methods

2.1. Subjects

The detailed information of subjects included in the present work had been described in our former work (Wu et al., 2009). Briefly, 218 treatment-naïve CHB patients (178 men/40 women) were enrolled in the present study. All enrolled patients were treated by IFNα-1b for six months. Response was identified as complete response (CR), partial response (PR) and non-response (NR). The study was performed after obtaining informed consent from all subjects, and approved by the ethics committee of Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

2.2. Genotyping

Genomic DNA was extracted from peripheral blood. Genotypes in HLA-A, HLA-B and HLA-C were detected by polymerase chain reaction-sequencing based typing (PCR-SBT) (Beijing Genomics Institute) and PCR-sequence specific primer (PCR-SSP) was used to detect genotypes of HLA-DQA1, HLA-DQB1 and HLA-DRB1 as shown elsewhere (Olerup et al., 1993; Olerup and Zetterquist, 1992). To distinguish DQA1*0301 from DQA1*0302, two pairs of primers were designed according to the sequence of the 3rd exon of DQA1, with the common sense primer, 5′-TGAGGTCACAGTGTTTTCCA-3′, and the specific antisense primer, 5′-TTGCAGTCATAAATCTCATCAG-3′, and 5-′TTGCAGTCATAAATCTCATCAT-3′ for non-DQA1 *0302/3 and DQA1*0302/3, respectively (231 bp). In the reaction system genotyping class II genes polymorphisms, positive internal control primers with concentration as one fifth of specific primers were pooled in order to eradicate pseudonegative possibilities. This control product was a 439 bp fragment of human growth hormone gene1, with primers 5′-CAGTGCCTTCCCAACCATTCCCTTA-3′ and 5′-ATCCACTCACGGATTTCTGTTGTGTTTC-3′, respectively.

2.3. Statistical analysis

We used 2×2 contingency tables for comparing HLA allele frequencies between the response group and non-response group. The EPI 6.0 version was used to calculate the statistical power. $P < 0.05$ was the criterion for statistical significance. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 12.0. Haplotype construction and analysis were performed by SHEsis online software (Shi and He, 2005).

Table 1
Frequencies distribution of common alleles in HLA-I and II genes in two efficacy groups.

Loci	Alleles	CR + PR ($n = 152$)	NR ($n = 66$)	P/Pc	OR	95%CI
A	*0201	46(0.151)	22(0.167)	0.69	1.12	0.62–2.02
	*0206	16(0.053)	8(0.061)	0.73	1.16	0.44–2.97
	*0207	19(0.062)	12(0.091)	0.29	1.50	0.66–3.37
	*1101	48(0.158)	25(0.189)	0.42	1.25	0.71–2.19
	*2402	47(0.155)	14(0.106)	0.18	0.65	0.33–1.27
	*3001	25(0.082)	8(0.061)	0.43	0.72	0.29–1.73
	*3101	16(0.053)	7(0.053)	0.99	1.01	0.37–2.69
	*3303	21(0.069)	9(0.068)	0.97	0.99	0.41–2.34
B	*1301	19(0.062)	7(0.053)	0.70	0.84	0.31–2.18
	*1302	23(0.076)	8(0.061)	0.57	0.79	0.31–1.92
	*1501	18(0.059)	10(0.076)	0.51	1.30	0.54–3.08
	*4001	27(0.089)	15(0.114)	0.42	1.32	0.64–2.68
	*4601	28(0.092)	19(0.144)	0.11	1.66	0.85–3.22
	*5101	21(0.069)	9(0.068)	0.97	0.99	0.41–2.34
C	*0102	42(0.138)	24(0.182)	0.24	1.39	0.77–2.48
	*0303	23(0.076)	15(0.114)	0.20	1.57	0.75–3.26
	*0304	28(0.092)	15(0.114)	0.49	1.26	0.62–2.56
	*0401	14(0.046)	9(0.068)	0.34	1.52	0.59–3.85
	*0602	39(0.128)	10(0.076)	0.11	0.56	0.25–1.20
	*0702	42(0.138)	14(0.106)	0.36	0.74	0.37–1.46
	*0801	31(0.102)	10(0.076)	0.39	0.72	0.32–1.59
	*1402	16(0.053)	7(0.053)	0.98	1.01	0.37–2.69
DQA1	*0101	21(0.069)	8(0.061)	0.74	0.87	0.34–2.14
	*0102	52(0.171)	24(0.182)	0.79	1.08	0.61–1.89
	*0103	21(0.069)	12(0.091)	0.43	1.35	0.60–2.98
	*0201	30(0.099)	16(0.121)	0.48	1.26	0.63–2.50
	*0301	29(0.095)	9(0.068)	0.36	0.69	0.30–1.59
	*0302	53(0.174)	28(0.212)	0.35	1.28	0.74–2.19
	*0501	53(0.174)	21(0.159)	0.70	0.90	0.50–1.61
	*0601	24(0.079)	5(0.038)	0.11	0.26	0.15–1.31
DQB1	*0201	40(0.132)	22(0.167)	0.34	1.32	0.72–2.41
	*0301/4	75(0.247)	24(0.182)	0.14	0.68	0.39–1.17
	*0302	17(0.056)	4(0.030)	0.25	0.53	0.15–1.71
	*0303	49(0.161)	34(0.258)	0.019/0.15	1.81	1.07–3.05
	*0502	21(0.069)	8(0.061)	0.74	0.87	0.34–2.14
	*0503	22(0.072)	8(0.061)	0.66	0.83	0.33–2.02
	*0601	22(0.072)	11(0.083)	0.69	1.17	0.51–2.61
	*0602	29(0.095)	12(0.091)	0.88	0.95	0.44–2.01
DRB1	*15	44(0.145)	16(0.121)	0.51	0.82	0.42–1.56
	*03	16(0.053)	7(0.053)	0.98	1.01	0.37–2.69
	*04	25(0.082)	6(0.045)	0.17	0.53	0.19–1.41
	*11	20(0.066)	9(0.068)	0.93	1.04	0.42–2.49
	*12	43(0.141)	18(0.136)	0.89	0.96	0.51–1.80
	*14	19(0.062)	2(0.015)	0.06	0.23	0.04–1.05
	*07	35(0.115)	14(0.106)	0.78	0.91	0.45–1.83
	*08	12(0.039)	12(0.091)	0.031/0.28	2.43	1.02–5.98
	*09	61(0.201)	31(0.235)	0.42	1.22	0.73–2.05

3. Results

After six months of therapy, 218 CHB patients were evaluated for the efficacy of IFNα by the combined assessment criteria. Since the CR rate was fairly low, CR group and PR group were combined into response group to be analyzed. The response rate was 69.7% (152/218), consisting of 17.4% of CR (38/218) and 52.3% of PR (114/218), and NR rate was 30.3% (66/218). There was no significant difference in distribution of age and gender among three groups, but the mean levels of ALT in the CR group and PR group were both higher than that in the NR group (188 IU/L in CR, 156 IU/L in PR and 101 IU/L in NR, $P = 0.001$).

Since the CR rate was fairly low, the CR group and PR group were combined into response group to be analyzed. We conducted genotyping experiments for the 6 HLA loci. Overall, we detected 10 HLA-DQA1 alleles, 14 HLA-DQB1 alleles, 14 HLA-DRB1 alleles, 24 HLA-A alleles, 45 HLA-B alleles and 33 HLA-C alleles. Table 1 showed common alleles with frequencies >5% in each

Table 2
Association of common haplotypes formed by HLA-A-B-C and HLA-DQA1-DQB1-DRB1 with efficacy of IFNα.

HLA	Haplotype	CR+PR (n = 152)	NR (n = 66)	P	OR	95%CI
A-B-C	*1101-*4601-*0102	4(0.013)	8(0.061)	0.009	4.84	1.29–19.48
	*3001-*1302-*0602	18(0.059)	3(0.023)	0.10	0.37	0.09–1.36
	*3303-*5801-*0302	11(0.036)	3(0.023)	0.57	0.62	0.13–2.44
DQA1-DQB1-DRB1	*0102-*0602-*15	13(0.043)	9(0.068)	0.27	1.64	0.63–4.22
	*0103-*0601-*08	8(0.026)	8(0.061)	0.10	2.39	0.79–7.18
	*0201-*0201-*07	16(0.053)	12(0.091)	0.13	1.80	0.77–4.16
	*0302-*0303-*09	27(0.089)	21(0.16)	0.031	1.94	1.01–3.73
	*0501-*0301/4-*11	12(0.039)	7(0.053)	0.52	1.36	0.47–3.83
	*0501-*0301/4-*12	14(0.046)	5(0.038)	0.70	0.82	0.25–2.49
	*0601-*0301/4-*12	18(0.059)	4(0.030)	0.21	0.50	0.14–1.60

HLA locus. Of these alleles, frequencies of HLA-DQB1*0303 and DRB1*08 in response group were clearly lower than those in NR group (P = 0.019, OR = 1.81, 95%CI = 1.07–3.15; P = 0.031, OR = 2.43, 95%CI = 1.02–5.98, respectively), while there were significant differences of other alleles between the two groups.

We next conducted haplotype analysis in HLA class I genes and class II genes. Table 2 showed common haplotypes with frequencies >3% formed by HLA-A-B-C and HLA-DQA1-DQB1-DRB1 genes. The result revealed that haplotype *1101-*4601-*0102 (HLA-A, -B, -C) and haplotype *0302-*0303-*09 (HLA-DQA1, DQB1, DRB1) were associated with non-response (1.3% vs 6.1%, P = 0.009, OR = 4.84, 95%CI = 1.29–19.48; 8.9% vs 16.0%, P = 0.031, OR = 1.94, 95%CI = 1.01–3.73, respectively).

4. Discussion

Our study reported some associated alleles and haplotypes of HLA class I and class II genes with efficacy of IFNα therapy. We reported that patients with HLA-DQB1*0303 or DRB1*08 alleles, and haplotype *1101-*4601-*0102 (HLA-A, B, C) or haplotype *0302-*0303-*09 (HLA-DQA1, DQB1, DRB1), were less responsive to IFNα treatment. However the sample size involved in the present study is not large enough, and it is possible that these findings may be incidental. Further validation studies in other ethnic groups and the confirmation of the present finding in a larger sample set are therefore required.

Nowadays standard IFN monotherapy is not the common way that hepatitis B is treated, as most patients are treated by IFN combined with a nucleoside analogue such as lamivudine. In the present study, we enrolled IFN monotherapy patients, because we thought monotherapy would be more suitable for genetic association studies. Patients received only one drug therapy, so the confounding factors would be less.

Our study was the first to test the association of HLA class I genes with efficacy of IFNα therapy. Although none of the alleles studied alone predicted response to treatment, we identified a haplotype *1101-*4601-*0102 constructed with HLA-A, -B, -C genes was associated with non-response to IFN therapy. Notably, in the present study, the HLA-A *1101, HLA-B *4601 and HLA-C *0102 were all susceptible to lower virological responses, although these differences were not significant. We concluded that this may be due to the cumulative effect of each allele, which when combined, showed significant differences.

In 2005, two studies in China reported that several HLA class II gene alleles were associated with efficacy of IFNα therapy (Chu et al., 2005; Han et al., 2005). But our study, however, did not confirm this result. The reason for these differences may be as follows: First, as discussed above, the sample size involved in the previous work was quite limited. Second, the distribution of gene polymorphism differed in different region. Although all Han Chinese involved in our sample were collected in Beijing, the other two studies collected samples from Shanghai and Shandong. Third, although our sample size was larger than in the previous works, there is the possibility that the present findings are incidental. So studies with even larger subjects are needed.

To explain fundamental reason of the association between HLA genes and efficacy, it is necessary to elucidate functions of allelic functions. Although current research provides lack of functional evidence, we can find some clues from some previously published observations. The HLA α chain and β chain construct a nine-pocket antigen binding pocket, its polymorphism is shown in peptide binding pocket region, and the deep pockets P1, P4, P6, P7 and P9 play important roles for antigen peptide binding (Gebe et al., 2002). The interaction between peptide skeleton, peptide lateral chains and HLA class II molecules play important role in maintaining the structure and stability of HLA class II molecules–antigen peptide complex and the ensuing T cells immune reaction. Within the DQ molecule, both genes encoding α and β chain contain the polymorphisms determining the peptide binding specificities, while in DR molecule only β chain coding gene contains polymorphisms. Summarizing the antigen binding pocket structures of molecules encoded by DQB1*0303 allele, we found a common ground for them that the amino acid sequence of P6 is Tyr-Tyr-Arg, P7 is Tyr-Tyr-Val-Arg-Thr, and P9 is Tyr-Tyr-Tyr-Ala-Ala/Asp. Compared with other DQB1 alleles, they are rich of tyrosine amino residues, which might be a hint that the structures rich of tyrosine are associated with persistence of viral antigen peptides.

Although there is no evidence supporting this hypothesis, the chemical and geometric properties of molecules encoded by different DQB1 and DRB1 alleles are significantly distinct, that probably affects the types and affinities of antigen peptide bound by HLA-DQ, DR molecules, stabilities of the DQ/DR–antigen peptide complex, and interaction of the complex with the T cell receptor. A study published in 2005 provides a wonderful example for testing this model. Godkin et al. (2005) demonstrated that the ability of viral peptides to bind to particular HLA glycoproteins are different which provided an answer to internal mechanism of the association of HLA class II gene polymorphism with the outcome of HBV infection and response to vaccination.

Briefly, polymorphisms of HLA genes are important host genetic markers affecting the efficacy of IFNα therapy. However there are still some aspects to be cleared and modified in the future. First of all, a larger pharmocogenetic study should be carried out since there were not sufficient individuals treated by IFN in this study. Secondly, nucleotide analogue drug has become a first line drug for HBV infection therapy, but we have to admit that neither nucleotide analogue nor combined therapy was studied.

Conflict of interests

The authors declare that they have no competing interests. This manuscript has not been published in whole or in part nor is it being considered for publication elsewhere.

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References

Becquemont, L., 2010. HLA: a pharmacogenomics success story. Pharmacogenomics 11, 277–281.

Cao, T., Desombere, I., Vanlandschoot, Sallberg, M., Leroux-Roels, G., 2002. Characterization of HLA DR13-restricted CD4(+) T cell epitopes of hepatitis B core antigen associated with self-limited, acute hepatitis B. J. Gen. Virol. 83, 3023–3033.

Chu, R.H., Ma, L.X., Wang, G., Shao, L.H., 2005. Influence of HLA-DRB1 alleles and HBV genotypes on interferon-alpha therapy for chronic hepatitis B. World J. Gastroenterol. 11, 4753–4757.

Gebe, J.A., Swanson, E., Kwok, W.W., 2002. HLA class II peptide-binding and autoimmunity. Tissue Antigens 59, 78–87.

Godkin, A., Davenport, M., Hill, A.V., 2005. Molecular analysis of HLA class II associations with hepatitis B virus clearance and vaccine nonresponsiveness. Hepatology 41, 1383–1390.

Han, Y.N., Yang, J.L., Zheng, S.G., Tang, Q., Zhu, W., 2005. Relationship of human leukocyte antigen class II genes with the susceptibility to hepatitis B virus infection and the response to interferon in HBV-infected patients. World J. Gastroenterol. 11, 5721–5724.

King, J.K., Yeh, S.H., Lin, M.W., Liu, C.J., Lai, M.Y., Kao, J.H., Chen, D.S., Chen, P.J., 2002. Genetic polymorphisms in interferon pathway and response to interferon treatment in hepatitis B patients: a pilot study. Hepatology 36, 1416–1424.

Klein, J., Sato, A., 2000. The HLA system. First of two parts. N. Engl. J. Med. 343, 702–709.

Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., LeVine, R., McEwan, P., McKernan, K., Meldrim, J., Mesirov, J.P., Miranda, C., Morris, W., Naylor, J., Raymond, C., Rosetti, M., Santos, R., Sheridan, A., Sougnez, C., Stange-Thomann, N., Stojanovic, N., Subramanian, A., Wyman, D., Rogers, J., Sulston, J., Ainscough, R., Beck, S., Bentley, D., Burton, J., Clee, C., Carter, N., Coulson, A., Deadman, R., Deloukas, P., Dunham, A., Dunham, I., Durbin, R., French, L., Grafham, D., Gregory, S., Hubbard, T., Humphray, S., Hunt, A., Jones, M., Lloyd, C., McMurray, A., Matthews, L., Mercer, S., Milne, S., Mullikin, J.C., Mungall, A., Plumb, R., Ross, M., Shownkeen, R., Sims, S., Waterston, R.H., Wilson, R.K., Hillier, L.W., McPherson, J.D., Marra, M.A., Mardis, E.R., Fulton, L.A., Chinwalla, A.T., Pepin, K.H., Gish, W.R., Chissoe, S.L., Wendl, M.C., Delehaunty, K.D., Miner, T.L., Delehaunty, A., Kramer, J.B., Cook, L.L., Fulton, R.S., Johnson, D.L., Minx, P.J., Clifton, S.W., Hawkins, T., Branscomb, E., Predki, P., Richardson, P., Wenning, S., Slezak, T., Doggett, N., Cheng, J.F., Olsen, A., Lucas, S., Elkin, C., Uberbacher, E., Frazier, M., Gibbs, R.A., Muzny, D.M., Scherer, S.E., Bouck, J.B., Sodergren, E.J., Worley, K.C., Rives, C.M., Gorrell, J.H., Metzker, M.L., Naylor, S.L., Kucherlapati, R.S., Nelson, D.L., Weinstock, G.M., Sakaki, Y., Fujiyama, A., Hattori, M., Yada, T., Toyoda, A., Itoh, T., Kawagoe, C., Watanabe, H., Totoki, Y., Taylor, T., Weissenbach, J., Heilig, R., Saurin, W., Artiguenave, F., Brottier, P., Bruls, T., Pelletier, E., Robert, C., Wincker, P., Smith, D.R., Doucette-Stamm, L., Rubenfield, M., Weinstock, K., Lee, H.M., Dubois, J., Rosenthal, A., Platzer, M., Nyakatura, G., Taudien, S., Rump, A., Yang, H., Yu, J., Wang, J., Huang, G., Gu, J., Hood, L., Rowen, L., Madan, A., Qin, S., Davis, R.W., Federspiel, N.A., Abola, A.P., Proctor, M.J., Myers, R.M., Schmutz, J., Dickson, M., Grimwood, J., Cox, D.R., Olson, M.V., Kaul, R., Raymond, C., Shimizu, N., Kawasaki, K., Minoshima, S., Evans, G.A., Athanasiou, M., Schultz, R., Roe, B.A., Chen, F., Pan, H., Ramser, J., Lehrach, H., Reinhardt, R., McCombie, W.R., de la Bastide, M., Dedhia, N., Blöcker, H., Hornischer, K., Nordsiek, G., Agarwala, R., Aravind, L., Bailey, J.A., Bateman, A., Batzoglou, S., Birney, E., Bork, P., Brown, D.G., Burge, C.B., Cerutti, L., Chen, H.C., Church, D., Clamp, M., Copley, R.R., Doerks, T., Eddy, S.R., Eichler, E.E., Furey, T.S., Galagan, J., Gilbert, J.G., Harmon, C., Hayashizaki, Y., Haussler, D., Hermjakob, H., Hokamp, K., Jang, W., Johnson, L.S., Jones, T.A., Kasif, S., Kaspryzk, A., Kennedy, S., Kent, W.J., Kitts, P., Koonin, E.V., Korf, I., Kulp, D., Lancet, D., Lowe, T.M., McLysaght, A., Mikkelsen, T., Moran, J.V., Mulder, N., Pollara, V.J., Ponting, C.P., Schuler, G., Schultz, J., Slater, G., Smit, A.F., Stupka, E., Szustakowski, J., Thierry-Mieg, D., Thierry-Mieg, J., Wagner, L., Wallis, J., Wheeler, R., Williams, A., Wolf, Y.I., Wolfe, K.H., Yang, S.P., Yeh, R.F., Collins, F., Guyer, M.S., Peterson, J., Felsenfeld, A., Wetterstrand, K.A., Patrinos, A., Morgan, M.J., de Jong, P., Catanese, J.J., Osoegawa, K., Shizuya, H., Choi, S., Chen, Y.J., International Human Genome Sequencing Consortium, 2001. Initial sequencing and analysis of the human genome. Nature 409, 860–921.

Lok, A.S., Heathcote, E.J., Hoofnagle, J.H., 2001. Management of hepatitis B: 2000–summary of a workshop. Gastroenterology 120, 1828–1853.

Olerup, O., Aldener, A., Fogdell, A., 1993. HLA-DQB1 and -DQA1 typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours. Tissue Antigens 41, 119–134.

Olerup, O., Zetterquist, H., 1992. HLA-DR typing by PCR amplification with sequence-specific primers (PCR-SSP) in 2 hours: an alternative to serological DR typing in clinical practice including donor-recipient matching in cadaveric transplantation. Tissue Antigens 39, 225–235.

Ormeci, N., 2003. Short- and long-term effects of treatment of chronic hepatitis B and delta virus by IFN. Fundam. Clin. Pharmacol. 17, 651–658.

Papatheodoridis, G.V., Hadziyannis, S.J., 2004. Review article: current management of chronic hepatitis B. Aliment. Pharmacol. Ther. 19, 25–37.

Rehermann, B., Nascimbeni, M., 2005. Immunology of hepatitis B virus and hepatitis C virus infection. Nat. Rev. Immunol. 5, 215–229.

Saracco, G., Rizzetto, M., 1997. A practical guide to the use of interferons in the management of hepatitis virus infections. Drugs 53, 74–85.

Shi, Y.Y., He, L., 2005. SHEsis, a powerful software platform for analyses of linkage disequilibrium, haplotype construction, and genetic association at polymorphism loci. Cell Res. 15, 97–98.

Urbani, S., Boni, C., Amadei, B., Fisicaro, P., Cerioni, S., Valli, M.A., Missale, G., Ferrari, C., 2005. Acute phase HBV-specific T cell responses associated with HBV persistence after HBV/HCV coinfection. Hepatology 41, 826–831.

Wu, X., Zhu, X., Zhu, S., Li, J., Ma, J., Li, Z., Li, H., Liu, Y., 2009. A pharmacogenetic study of polymorphisms in interferon pathway genes and response to interferon-alpha treatment in chronic hepatitis B patients. Antiviral Res. 83, 252–256.