Antiviral Research 83 (2009) 252–256

Contents lists available at ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

A pharmacogenetic study of polymorphisms in interferon pathway genes and response to interferon-α treatment in chronic hepatitis B patients☆

Xiaopan Wu[a], Xilin Zhu[a], Shuying Zhu[a], Jingyun Li[a], Juan Ma[a], 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, PR China
[b] Department of Infectious Disease, Affiliated Youan Hospital, Capital University of Medical Science, PR China
[c] Department of Epidemiology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences; School of Basic Medicine, Peking Union Medical College, PR China

ARTICLE INFO

Article history:
Received 23 March 2009
Received in revised form 5 June 2009
Accepted 10 June 2009

Keywords:
Chronic hepatitis B
Interferon-α therapy
Interferon pathway gene
Single nucleotide polymorphism
Pharmacogenetic study

ABSTRACT

Certain host genetic polymorphisms in interferon (IFN) signaling pathway genes are reported to be associated with response to IFNα therapy. We studied 10 single nucleotide polymorphisms (SNPs) in IFN signaling pathway genes to examine their associations with response to IFN treatment in chronic hepatitis B (CHB) patients. Two hundred and forty-six IFNα treatment-naïve CHB patients were enrolled for the present study; all received treatment with IFNα alone for 6 months, and the efficacy of the therapy was examined. Ten SNPs in 8 IFN signaling pathway genes were genotyped using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) protocol. There were no significant differences in allele frequencies and genotype distributions of the 10 SNPs between the response and non-response groups that underwent IFNα therapy. However, 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 (16.1% *vs.* 8.7%, $p = 0.015$). Our study suggested that patients with a G-T-G-A *OAS* haplotype were less responsive to IFNα treatment.

1. Introduction

Hepatitis B virus (HBV) infection is a serious public health problem all over the world. HBV infection results in 0.5–1.2 million deaths per year, which is mainly caused by its clinical consequences such as chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (Ganem and Prince, 2004; Rehermann and Nascimbeni, 2005). Interferon alfa (IFNα) has been a first-line drug for hepatitis B due to its antiviral and immunomodulatory activities (Saracco and Rizzetto, 1997). However, successful response to IFNα therapy occurs in only 25–50% of CHB patients treated with IFNα for 4–6 months (Gish, 2005). Considering the length, side effects, and costs of IFNα treatment, accurate pre-treatment prediction of response to therapy is very important. Studies have reported that high alanine aminotransferase (ALT) levels (>200 IU/L), low serum HBV DNA levels (<100 pg/mL), female gender, and HBV genotype B are associated with good response to IFNα therapy; however, the biological mechanisms underlying variations in response to IFNα therapy are not well understood (Hoofnagle and di Bisceglie, 1997; Kao et al., 2000; Lin and Keeffe, 2001). With the advances in pharmacogenetics, there is accumulating information indicating that single nucleotide polymorphisms (SNPs) in drug-metabolism genes are closely associated with the metabolism and efficacy of drugs (Ahmadi et al., 2005). The first pharmacogenetic study on IFNα therapy and its effects on hepatitis B patients was conducted by King et al. It focused on 22 genetic polymorphisms in interferon pathway genes and identified an intron polymorphism (rs3759756) in the gene encoding eukaryotic translation initiation factor 2 subunit 1-alpha (*EIF2S1*), which may influence IFN response in hepatitis B patients (King et al., 2002).

Through the IFNα signaling pathway, IFNα promotes viral control by immune regulation and suppression of HBV infection. The IFNα signaling pathway genes include the JAK-STAT pathway genes and interferon-stimulating genes (ISGs) such as myxovirus resistance 1 (*MxA*), eukaryotic translation initiation factor 2-alpha kinase 2 (*PKR*), 2′,5′-oligoadenylate synthetase (*OAS*), adenosine deaminase (*ADAR*), etc. (Kalvakolanu, 2003; Samuel, 2001; Thomas et al., 2003).

☆ Parts of the present study have been presented as an abstract in the Hong Kong–Shanghai International Liver Congress in June 2008, Hong Kong, China.

* Corresponding author at: 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. Tel.: +86 10 65296419; fax: +86 10 65296419.

** Corresponding author at: Department of Epidemiology, Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences, 5 Dongdan 3 Tiao, Beijing 100005, PR China.

E-mail addresses: wuxiaopan1984@tom.com (X. Wu), lihui99360@sohu.com (H. Li), liuyingpumc@yahoo.com (Y. Liu).

0166-3542/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.antiviral.2009.06.003

We performed a nested case-control study for which we recruited treatment-naïve CHB patients from the Beijing Youan Hospital in northern China. The enrolled patients were treated with IFNα-1b alone for 6 months and then followed up for 6 months to evaluate the therapeutic effects. We then performed an association study of 10 polymorphisms in interferon pathway genes and response to IFNα treatment. The 10 SNPs were rs3759756 in *EIF2S1* gene, which were reported to be associated with IFN response in Taiwan Han Chinese (King et al., 2002) and 9 tag-SNPs in 7 IFN pathway genes.

2. Materials and methods

2.1. Subjects

The subjects enrolled in the present study were 246 Han Chinese treatment-naïve CHB patients (207 men/39 women) recruited from the Beijing Youan Hospital between November 2001 and October 2003. The patients were diagnosed as having chronic hepatitis B if their serum levels of ALT and aspartate aminotransferase (AST) were continuously abnormal and if they were HBsAg- and/or HBeAg-seropositive, and anti-HBs-seronegative 6 months after acute infection. Patients were excluded if: (1) there was evidence of past or current infection with other hepatitis viruses or hepatitis not caused by HBV; (2) they had cirrhosis or hepatocellular carcinoma; or (3) they were not of Han ethnicity. All enrolled patients were treated with IFNα-1b (Sanyuan genetic company, Beijing, China) alone, with an initial dose of 3–5 MU/d for 2 weeks, followed by 3–5 MU dieb. alt. for 6 months. Patients were then followed up for 6 months to evaluate the therapeutic effects. Complete response (CR) was confirmed if the following evidences were present: the patients had normal ALT and AST levels, they were HBV-DNA-negative, and HBeAg negative after therapy, or they were anti-HBe-seropositive. Partial response (PR) was confirmed if the following criteria were met: only ALT and AST levels return to normal or the patient showed negative HBeAg after therapy but was positive for HBV-DNA. Patients who did not satisfy any of the abovementioned criteria were categorized as non-responding (NR) patients. The study was carried out in accordance with the guidelines of the Helsinki Declaration after obtaining informed consent from all the subjects and was approved by the ethics committee of the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

2.2. Serological testing

Enzyme-linked immunosorbent assay (ELISA) was performed for the detection of serum HBsAg, anti-HBs, HBeAg, anti-HBe, and anti-HBc (IMX; Abbott Diagnostics, North Chicago, IL). The ALT and AST levels were measured by a continuous monitoring assay and found to be <40 IU/L, which is within the normal range of values.

2.3. SNP selection and genotyping

Genomic DNA was extracted from peripheral blood by using a salting-out protocol. The 10 SNPs (rs2252930 in *IFNAR1*; rs3177979 in *OAS1*; rs1293747 in *OAS2*; rs4767043 in *OAS3*; rs10849829 in *OASL*; rs17127090 in Janus kinase 1 (*JAK1*); rs3738032, rs1127314, and rs3766924 in *ADAR*; and rs3759756 in *EIF2S1*) selected for the present study are recorded in the public dbSNP database. The SNP ID numbers and detailed sequence information are

Table 1
Outline of SNP genotyping.

Loci	Primer sequences (5′-3′)	Tm (°C)[a]	PCR product (bp)	Restriction enzyme	Genotype
rs2252930	F: GTTGCCACTGAGCCCTATTA R: CCTATTCTTGTCTTCCCCAC	60	431	Van91I	GG: 431bp CG: 431bp + 150bp + 281bp CC: 150bp + 281bp
rs3177979	F: TGGATCACTCACTGTGCTTG R: CATGTGTTCCAATGTAACCA	58	333	RsaI	GG: 333bp AG: 333bp + 271bp + 62bp AA: 271bp + 62bp
rs1293747	F: TGGTTTCACATTTCAGGGAG R: TTCATTTGGGTCAGGCGTTG	60	491	BanII	TT: 491bp CT: 491bp + 283bp + 208bp CC: 283bp + 208bp
rs4767043	F: AGTGTCTCCCTTTGTCATCC R: ATCTTGGTATCCCAGTGTCC	62	442	HhaI	CC: 442bp CG: 442bp + 272bp + 170bp GG: 272bp + 170bp
rs10849829	F: ACCTTCTCCAAAGAGCAACT R: TGGATGTGAGGATACGCAGT	60	412	HaeIII	AA: 412bp AG: 412bp + 144bp + 268bp GG: 144bp + 268bp
rs17127090	F: TTCAAACAGCAAACCCAA R: ATGATAACCTCGTTCCTT	50	109	HaeIII	GG: 109bp CG: 109bp + 70bp + 39bp CC: 70bp + 39bp
rs3738032	F: GCCCTCCTTCTACAGTCAT R: CAGCCAACAGAGTCAACCT	55	403	HhaI	AA: 403bp AG: 403bp + 262bp + 141bp GG: 262bp + 141bp
rs1127314	F: CAGGATGACACAGACCACTT R: TGCCCTTTCACCCACAACTA	60	503	MspI	TT: 503bp CT: 503bp + 235bp + 268bp CC: 235bp + 268bp
rs3766924	F: TGTTTACCTAGCCTGGTTTC R: TCTTTGCTCAGTCTGGGATT	60	362	AccB1I	AA: 362bp AG: 362bp + 276bp + 86bp GG: 276bp + 86bp
rs3759756	F: TCATTGCTTCACTGTGCCCT R: TTGTGTTCCAGTCCTTGCTC	60	695	SspI	TT: 695bp GT: 695bp + 520bp + 175bp GG: 520bp + 175bp

[a] Tm, annealing temperature

Table 2
Genotype distributions and allelic frequencies of SNPs in IFN pathway genes in chronic hepatitis B patients treated with IFNα.

SNPs	CR + PR $n = 169$(%)	NR $n = 77$(%)	χ^2	p	OR	95%CI
IFNAR1 rs2252930						
C/C	89(52.7)	42(54.5)				
C/G	70(41.4)	27(35.1)	2.02	0.36		
G/G	10(5.9)	8(10.4)				
C	248(73.4)	111(72.1)	0.09	0.76	0.93	0.61–1.44
G	90(26.6)	43(27.9)				
OAS1 rs3177979						
A/A	75(44.4)	32(41.6)				
A/G	78(46.2)	39(50.6)	0.49	0.78		
G/G	16(9.5)	6(7.8)				
A	228(67.5)	103(66.9)	0.016	0.90	0.97	0.65–1.46
G	110(32.5)	51(33.1)				
OAS2 rs1293747						
C/C	42(24.9)	13(16.9)				
C/T	79(46.7)	38(49.4)	2.08	0.35		
T/T	48(28.4)	26(33.8)				
C	163(48.2)	64(41.6)	1.89	0.17	0.76	0.52–1.12
T	175(51.8)	90(58.4)				
OAS3 rs4767043						
C/C	24(14.2)	14(18.2)				
C/G	73(43.2)	27(35.1)	1.61	0.45		
G/G	72(42.6)	36(46.8)				
C	121(35.8)	55(35.7)	0.0003	0.99	0.99	0.67–1.48
G	217(64.2)	99(64.3)				
OASL rs10849829						
A/A	81(47.9)	41(53.2)				
A/G	74(43.8)	31(40.3)	0.68	0.71		
G/G	14(8.3)	5(6.5)				
A	236(69.8)	113(73.4)	0.65	0.42	1.19	0.78–1.82
G	102(30.2)	41(26.6)				
JAK1 rs17127090						
C/C	86(50.9)	37(48.1)				
C/G	75(44.4)	36(46.8)	0.17	0.92		
G/G	8(4.7)	4(5.2)				
C	247(73.1)	110(71.4)	0.14	0.70	0.92	0.60–1.40
G	91(26.9)	44(28.6)				
ADAR rs3738032						
G/G	112(66.3)	56(72.7)				
G/A	55(32.5)	17(22.1)	5.79	0.06		
A/A	2(1.2)	4(5.2)				
G	279(82.5)	129(83.8)	0.11	0.74	1.09	0.65–1.82
A	59(17.5)	25(16.2)				
ADAR rs1127314						
T/T	74(43.8)	38(49.4)				
T/C	81(47.9)	33(42.9)	0.67	0.72		
C/C	14(8.3)	6(7.8)				
T	229(67.8)	109(70.8)	0.45	0.50	1.15	0.76–1.75
C	109(32.2)	45(29.2)				
ADAR rs3766924						
G/G	114(67.5)	48(62.3)				
G/A	48(28.4)	26(33.8)	0.72	0.70		
A/A	7(4.1)	3(3.9)				
G	276(81.7)	122(79.2)	0.40	0.52	0.86	0.53–1.38
A	62(18.3)	32(20.8)				
EIF2S1 rs3759756						
A/A	155(91.7)	69(89.6)				
A/G	14(8.3)	7(9.1)	2.26	0.32		
G/G	0	1(1.3)				
A	324(95.9)	145(94.2)	0.69	0.41	0.70	0.29–1.65
G	14(4.1)	9(5.8)				

NR, non-response; CR, complete response; PR, partial response

available at http://www.ncbi.nlm.nih.gov/SNP/. The 10 SNPs were genotyped using a polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) protocol. The details of the PCR-RFLP genotyping experiments are summarized in Table 1.

2.4. Statistical analysis

By using the χ^2 test, we tested whether the genotype distributions for the studied SNPs were in the Hardy–Weinberg equilibrium (HWE). We used 2×2 or 2×3 contingency tables for comparing

allele and genotype frequencies between the response group and the non-response group. The EPI version 6.0 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. We estimated linkage disequilibrium (LD) values (D′), r^2 values, and haplotypes by using the online software SHEsis (Shi and He, 2005).

3. Results

After 6 months of therapy, we evaluated the efficacy of IFNα in the 246 patients on the basis of the criteria for combined assessment. The response rate was 68.7% (169/246), with 16.3% of the patients showing CR (40/246) and 52.4% showing PR (129/246); and the NR rate was 31.3% (77/246). There was no significant difference in the distribution of age and gender among the 3 groups, but the mean levels of ALT in the CR and PR groups were both higher than that in the NR group (189.0 IU/L in CR, 156.5 IU/L in PR, and 100.3 IU/L in NR, $p = 0.001$).

Since the CR rate was fairly low, the CR and PR groups were combined into a single response group for analysis. We conducted genotyping experiments for the 10 polymorphisms. Genotype distributions of the studied SNPs were in HWE except for the SNP rs4767043 in the *OAS3* gene, which deviated slightly from the HWE in the non-response patient group ($p = 0.04$). There were no significant differences in allele frequencies and genotype distributions of the 10 SNPs studied between the response and non-response groups (Table 2). We also compared the allele frequencies and genotype distributions of these SNPs in the CR and NR groups, or in CR and PR + NR groups, and the results were still negative (data not shown).

We analyzed the degree of LD for 4 SNPs in the *OAS1*, *OAS2*, *OAS3*, and *OASL* genes, and 3 SNPs in the *ADAR* gene. There was no apparent LD (D′ < 0.462, $r^2 < 0.089$ for the *OAS* genes and D′ < 0.836, $r^2 < 0.28$ for the *ADAR* gene). Next, we conducted a haplotype analysis of the *OAS* genes and the *ADAR* gene. For the 3 SNPs in the *ADAR* gene, there were 4 common haplotypes with a frequency >5%; however, there were no significant differences between the response and non-response groups with respect to the frequency of these haplotypes. For the *OAS* SNPs, Table 3 shows 6 common haplotypes that were the result of these 4 SNPs and had a frequency > 5%. The frequency of the G-T-G-A haplotype in the non-response group was significantly higher than that in the response group (16.1% *vs.* 8.7%, $p = 0.015$). We also compared the G-T-G-A haplotype frequency in the CR and NR groups, or in the CR and PR + NR groups. In the CR and NR groups, although the sample size was relatively small, the frequency of the G-T-G-A haplotype in the NR group was also significantly higher than that in the CR group (16.1% *vs.* 6.4%, $p = 0.028$). There was a borderline significant difference between the CR and PR + NR groups (13.2% in the PR + NR group *vs.* 6.4% in CR group, $p = 0.08$).

4. Discussion

In the present study, we found that patients with high levels of ALT were more responsive to IFN treatment; this observation is in agreement with previous reports (Hoofnagle and di Bisceglie, 1997; Lin and Keeffe, 2001). Although none of the 10 SNPs when studied alone predicted response to treatment, we identified a haplotype, namely, G-T-G-A, which results from SNPs in the *OAS1*, *OAS2*, *OAS3*, and *OASL* genes, that was associated with response to IFN therapy. However, the sample size involved in the present study is not large enough, and it is possible that these findings may be incidental. Therefore, it is necessary to perform further studies in other ethnic groups and to confirm the present findings in a larger sample set.

The genotype distribution of the SNP rs4767043 in *OAS3* deviated from the HWE in non-response patients. It is necessary to examine whether HWE is followed in normal control subjects. In the present association study, however, both the cases and controls were CHB patients. On the other hand, the purpose to apply HWE is to eliminate the possibility of genotyping errors in molecular genetics studies. For genotyping quality control, 20% of the samples were randomly genotyped again by a different researcher, and we obtained 100% identical results.

Till date, there have been few studies on the relationship between host genetic factors and response to IFN treatment. In 2002, King et al. carried out the first and most systematic pharmacogenetic study (King et al., 2002). They included all the available SNPs located in the promoter region, regulatory region, and exons of IFN pathway genes; and identified rs3759756 in the *EIF2S1* gene as a better marker for IFN response than the HBV DNA level ($p = 0.023$ *vs.* $p = 0.033$). They also revealed borderline significance for the *MxA* G-88T polymorphism ($p = 0.061$). In 2007, Kong et al. found that the genotype distribution of the *MxA* G-88T polymorphism differed significantly between IFN-responders and IFN-non-responders, and the induction of *MxA* mRNA by IFNα might predict sustained virological responses to IFNα treatment in CHB patients (Kong et al., 2007). To the best of our knowledge, these 2 studies are the only pharmacogenetic studies on IFN pathway genes and response to IFN therapy, and rs3759756 in the *EIF2S1* gene and *MxA* G-88T polymorphism are the only 2 SNPs in the IFN pathway genes found to be associated with response to IFN therapy. Some other studies have revealed that genetic structural differences (short tandem repeat markers)(Chen et al., 2006), *IL-1β* gene polymorphisms (Chan et al., 2006), and *HLA-II* gene polymorphisms (Chu et al., 2005; Han et al., 2005) are associated with response to IFN treatment in CHB patients. In all the above studies, the sample size was limited; Chu et al.'s study had the biggest sample (Chu et al., 2005), which included 126 CHB patients. With such a limited sample size, the statistical power for detecting a twofold association between the presence of an allele and response to IFN treatment were considerably low (presuming a 95% confidence interval, a responder/non-responder ratio of 1/1, and a minor allele frequency of 20%, the statistical power is about 35% in 138 persons). In our present study, we replicated the genotyping of rs3759756 in the *EIF2S1* gene, and since other potential functional SNPs in the study of King et al. showed no significant differences, we chose 9 other tag-SNPs in 7 IFN pathway genes (which have not been studied before) to examine whether these SNPs are associated with response to IFN treatment. The results showed that none of the 10 SNPs predicted response to treatment. There is another SNP, namely, *MxA* G-88T, which predicted response to treatment in Kong et al.'s study (Kong et al., 2007), but in our previous study, this SNP did not predict response to treatment (unpublished data). The reasons for these differences may be as follows: first, as discussed above, since the sample sizes in the previous studies were limited, their findings may be incidental. Second, the distribution of gene polymorphism may differ not only across different ethnicities but also among people of the same ethnicity from different regions. Although all subjects in the abovementioned studies were Han Chinese, our samples were collected from northern Han Chinese subjects, while the other 2 studies collected samples from south China. Third, although our

Table 3
Common haplotypes resulting from SNPs rs3177979 in *OAS1*, rs1293747 in *OAS2*, rs4767043 in *OAS3*, and rs10849829 in *OASL*.

Haplotypes	Non-response *n* (%)	Response *n* (%)	*p*-value	OR (95%CI)
A-C-C-A	18(11.4)	32(9.4)	0.51	1.23(0.66-2.28)
A-C-G-A	22(14.2)	55(16.2)	0.54	0.85(0.49–1.45)
A-C-G-G	11(7.1)	37(11.1)	0.16	0.61(0.30–1.22)
A-T-G-A	25(16.4)	43(12.9)	0.31	1.32(0.77–2.25)
G-T-C-A	14(9.1)	21(6.2)	0.25	1.51(0.75–3.07)
G-T-G-A	25(16.1)	29(8.7)	0.015	2.01(1.13–3.58)

sample size was larger than that in the previous studies, this is not sufficient, and there is a possibility that the present findings are incidental. Therefore, studies involving even larger sample sizes are needed.

In contrast to the limited number of pharmacogenetic studies on IFN therapy in CHB patients, there are many more studies on chronic hepatitis C patients; however, the results are controversial. In 2008, Su et al. suggested that 3 *OASL* SNPs are involved in host response to IFN-based therapy in hepatitis C patients (Su et al., 2008). In the same year, Morgan et al. selected 8 SNPs on the basis of previously reported associations with treatment response in certain hepatitis C patients. However, they found no significant association between genotypes for any individual SNP, except for an ACC *IL10* promoter diplotype, which was associated with sustained virological responses (Morgan et al., 2008). In the present study, we identified a G-T-G-A haplotype resulting from 4 SNPs in the *OAS* genes to be associated with lower virological responses. The interferon-induced 2′-5′-oligoadenylate synthetases (*OAS*) catalyze the synthesis of oligoadenylates of the general structure $ppp(A2'p)_nA$, commonly abbreviated as 2-5A, and the IFN-inducible 2-5A response leading to the degradation of RNA. These effects are important in the anti-viral response (Samuel, 2001). The findings therefore indicate that the *OAS* genes contribute to genetic susceptibility to viral infection. The human *OAS* family contains the *OAS1*, *OAS2*, *OAS3*, and *OASL* genes (Rebouillat and Hovanessian, 1999), and the 4 *OAS* genes are all located on chromosome 12q24. Notably, in the present study, the rs3177979G, rs1293747T, rs4767043G, and rs10849829A alleles, which were in the *OAS1*, *OAS2*, *OAS3*, and *OASL* genes respectively, 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 on different genes in the *OAS* gene family, which when combined, showed significant differences.

In summary, we have shown that patients with a G-T-G-A *OAS* haplotype were less responsive to IFN treatment. However, we could not find any single SNP associated with virological responses.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

We are grateful to all the subjects who participated in this study. This work was supported by grants from the National Basic Research Program of China (973 Program) (No. 2007CB512806), the National High Technology Research and Development Program of China (863 Program) (No. 2006AA02A4100), the Beijing Municipal Government Commission for Science & Technology (No. H020920020590) and the Science Fund for Creative Research Groups (No. 30421003).

References

Ahmadi, K.R., Weale, M.E., Xue, X.Y., Soranzo, N., Yarnall, D.P., Briley, J.D., Maruyama, Y., Kobayashi, M., Wood, N.W., Spurr, N.K., et al., 2005. A single-nucleotide polymorphism tagging set for human drug metabolism and transport. Nat Genet 37 (1), 84–89.

Chan, H.L., Tse, A.M., Zhang, M.D., Wong, V.W., Chim, A.M., Hui, A.Y., Sung, J.J., 2006. Genetic polymorphisms of interleukin-1-beta in association with sustained response to anti-viral treatment in chronic hepatitis B in Chinese. Aliment Pharmacol Ther 23 (12), 1703–1711.

Chen, P.J., Lin, C.G., Lin, F.Y., Chen, E., Wu, L.S., 2006. Genetic structural differences between responders and non-responders to interferon therapy for chronic hepatitis-B patients. J Hum Genet 51 (11), 984–991.

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 (30), 4753–4757.

Ganem, D., Prince, A.M., 2004. Hepatitis B virus infection–natural history and clinical consequences. N Engl J Med 350 (11), 1118–1129.

Gish, R.G., 2005. Current treatment and future directions in the management of chronic hepatitis B viral infection. Clin Liver Dis 9 (4), 541–565, v.

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 (36), 5721–5724.

Hoofnagle, J.H., di Bisceglie, A.M., 1997. The treatment of chronic viral hepatitis. N Engl J Med 336 (5), 347–356.

Kalvakolanu, D.V., 2003. Alternate interferon signaling pathways. Pharmacol Ther 100 (1), 1–29.

Kao, J.H., Wu, N.H., Chen, P.J., Lai, M.Y., Chen, D.S., 2000. Hepatitis B genotypes and the response to interferon therapy. J Hepatol 33 (6), 998–1002.

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 (6), 1416–1424.

Kong, X.F., Zhang, X.X., Gong, Q.M., Gao, J., Zhang, S.Y., Wang, L., Xu, J., Han, Y., Jin, G.D., Jiang, J.H., et al., 2007. MxA induction may predict sustained virologic responses of chronic hepatitis B patients with IFN-alpha treatment. J Interferon Cytokine Res 27 (9), 809–818.

Lin, O.S., Keeffe, E.B., 2001. Current treatment strategies for chronic hepatitis B and C. Annu Rev Med 52, 29–49.

Morgan, T.R., Lambrecht, R.W., Bonkovsky, H.L., Chung, R.T., Naishadham, D., Sterling, R.K., Fontana, R.J., Lee, W.M., Ghany, M.G., Wright, E.C., et al., 2008. DNA polymorphisms and response to treatment in patients with chronic hepatitis C: results from the HALT-C trial. J Hepatol 49 (4), 548–556.

Rebouillat, D., Hovanessian, A.G., 1999. The human 2′,5′-oligoadenylate synthetase family: interferon-induced proteins with unique enzymatic properties. J Interferon Cytokine Res 19 (4), 295–308.

Rehermann, B., Nascimbeni, M., 2005. Immunology of hepatitis B virus and hepatitis C virus infection. Nat Rev Immunol 5 (3), 215–229.

Samuel, C.E., 2001. Antiviral actions of interferons. Clin Microbiol Rev 14 (4), 778–809, table of contents.

Saracco, G., Rizzetto, M., 1997. A practical guide to the use of interferons in the management of hepatitis virus infections. Drugs 53 (1), 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 (2), 97–98.

Su, X., Yee, L.J., Im, K., Rhodes, S.L., Tang, Y., Tong, X., Howell, C., Ramcharran, D., Rosen, H.R., Taylor, M.W., et al., 2008. Association of single nucleotide polymorphisms in interferon signaling pathway genes and interferon-stimulated genes with the response to interferon therapy for chronic hepatitis C. J Hepatol 49 (2), 184–191.

Thomas, H., Foster, G., Platis, D., 2003. Mechanisms of action of interferon and nucleoside analogues. J Hepatol 39 (Suppl. 1), S93–S98.