Association Studies of Genetic Susceptibility to Hepatitis B and C in the US Population

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Background:

Hepatitis B and C are two major global public health problems. Of 2 billion people who have been infected with the hepatitis B virus (HBV), more than 350 million have chronic (lifelong) infections. There are about 170 million people worldwide who are infected with hepatitis C virus (HCV). Persistent carriage rates, which confer an increased risk of liver complications, liver failure, or end-stage carcinoma, are ~5-10% in hepatitis B, compared with ~75-85% in hepatitis C infection. Understanding why some individuals acquire and progress to chronic HBV and HCV infection, while others do not, is a priority in the prevention of these diseases.

Aims:

- Investigate the associations between candidate gene variants and risk for HBV and HCV infections.
- Investigate whether the above associations vary with age, sex, race/ethnicity, and other potential risk factors for HBV and HCV infection (such as illegal drug use and high-risk sexual behavior).

Methods:

Table 1. Demographic characteristic of NHANES III Participants with hepatitis B or C

Total number	7159
Sex (%)	
Male	3102 (43.3)
Female	4057 (56.7)
Age (%)	
12-19 yrs	1211 (16.9)
20-39 yrs	2597 (36.3)
40-59 yrs	1552 (21.7)
60+ yrs	1799 (25.1)
Race/Ethnicity (%)	
Non-Hispanic White	2630 (36.7)
Non-Hispanic Black	2108 (29.5)
Mexican-American	2073 (29.0)
Other	348 (4.9)
Serum hepatitis B core antibody (anti-HBc, %)	
Positive	500 (7.0)
Negative	6624 (93.0)
Serum hepatitis B surface antigen (HBsAg, %)	
Positive	30 (6.0)
Negative	469 (94.0)
Chronic hepatitis B (both anti-HBc and HBsAg are positive)	
Yes	30 (6.0)
No	468 (94.0)
Serum hepatitis C antibody (%)	
Positive	156 (2.2)
Negative	7122 (97.8)
Hepatitis C Virus RNA (%)	
Positive	114 (79.2)
Negative	30 (20.8)
Chronic hepatitis C (both Hepatitis C antibody and virus RNA are positive)	
Yes	114 (79.2)
No	30 (20.8)

Using genotyping data available from 7,159 participants aged 12 and older enrolled in phase 2 (1991-1994) of the Third National Health and Nutrition Examination Survey (NHANES III), we analyzed the associations between 77 genetic variants in 36 candidate genes and risk for HBV and HCV infections.

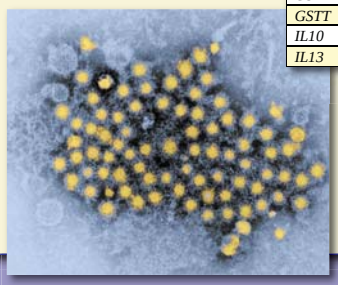
Phenotype Definitions:

- HBV infection
  - A positive test for serum hepatitis B core antibody (anti-HBc)
- Chronic HBV infection
  - Positive tests for both anti-HBc and serum hepatitis B surface antigen (HBsAg)
- HCV infection
  - A positive test for anti-HCV antibody
- Chronic HCV
  - Positive tests for both hepatitis C antibody and virus RNA

Due to small sample sizes, we were unable to examine the associations between the variants and persistence and progression to chronic HBV and HCV (Table 1, 2).

Table 2. List of genes tested for association with hepatitis B and C

Gene(s)	
ABCB1	*IL1B*
CAT	*IL4*
CCL5	*IL4R*
CCR2	*ITGA2*
CRP	*MBL2*
CXCL12	*NQO1*
CYP1A1	*NAT1*
CYP1A2	*NAT2*
CYP1B1	*NOS2A*
CYP2A6	*NOS3*
CYP2C19	*OGG1*
CYP2E1	*PON1*
CYP3A4	*PPARG*
FCGR2A	*TGFB1*
GSTM1	*TLR4*
GSTT	*TNF*
IL10	*VDR*
IL13	*XRCC1*



Results:

- ***HBV***
  - Genetic variants in four genes showed increased protection against HBV infection (Table 3)
    - *MBL2* (rs11003125, OR = 0.47, p = 0.003)
    - *NQO1* (rs34755915, OR = 0.05, p = 0.005)
    - *PPARG* (rs1801282, OR = 0.35, p = 0.007)
    - *XRCC1* (rs1001581, OR = 0.38, p = 0.004)
- ***HCV***
  - Polymorphisms in four genes appeared to be strongly protective against HCV infection (Table 4)
    - *CYP1A1* (rs2606345, OR = 0.44, p = 0.0008)
    - *CYP3A4* (rs2740574, OR = 0.24, p = <0.0001)
    - *MBL2* (rs1800451, OR = 0.35, p = 0.0040)
    - *TGFB1* (rs1800469, OR = 0.41, p = 0.0002)
  - Polymorphisms in four genes appeared to increase susceptibility to HCV infection
    - *CRP* (rs3093058, OR = 2.40, p = 0.005)
    - *CYP1A2* (rs4886406, OR = 1.77, p = 0.003)
    - *ITGA2* (rs1126643, OR = 3.02, p = 0.002)
    - *NAT2* (rs1801280, OR = 2.59, p = 0.002)

Table 3. Association of genotype and acquisition of HBV*

Gene	Variant	Genetic Model	Odds Ratio (CI)	p-Value
MBL2	rs11003125	CG	0.47 (0.27-0.79)	0.003
		CC/GG	1.00 (1.00-1.00)	
NQO1	rs34755915	AA/AG	0.05 (0.01-0.45)	0.005
		GG	1.00 (1.00-1.00)	
PPARG	rs1801282	GG/GC	0.35 (0.16-0.79)	0.007
		CC	1.00 (1.00-1.00)	
XRCC1	rs1001581	AA	0.38 (0.19-0.77)	0.004
		AG/GG	1.00 (1.00-1.00)	

*Adjustment for race/ethnicity, the number of sex partners, place of birth, CRP, serum ALT, serum AST and co-infection with HCV.

Table 4. Association of genotype and acquisition of HCV*

Gene	Variant	Genetic Model	Odds Ratio (CI)	p-Value
CRP	rs3093058	TT/TA	2.4 (1.25-4.59)	0.005
		AA	1.00 (1.00-1.00)	
CYP1A1	rs2606345	GT	0.44 (0.30-0.66)	0.0008
		GG/TT	1.00 (1.00-1.00)	
CYP1A2	rs4886406	GT	1.77 (1.20-2.62)	0.003
		GG/TT	1.00 (1.00-1.00)	
CYP3A4	rs2740574	CC/GA	0.24 (0.12-0.50)	<0.0001
		AA	1.00 (1.00-1.00)	
ITGA2	rs1126643	TT/TC	3.02 (1.42-6.42)	0.002
		CC	1.00 (1.00-1.00)	
MBL2	rs1800451	AA/AG	0.35 (0.17-0.74)	0.004
		GG	1.00 (1.00-1.00)	
NAT2	rs1801280	CT	2.59(1.35-4.95)	0.002
		CC/TT	1.00 (1.00-1.00)	
TGFB1	rs1800469	CT	0.41(0.25-0.67)	0.0002
		CC/TT	1.00 (1.00-1.00)	

*Adjustment for race/ethnicity, the number of sex partners, history of cocaine use, Marijuana use, CRP, Herpes simplex virus type 2 infection, serum ALT and serum AST.

Conclusion:

- Genetic polymorphisms in *MBL2, NQO1, PPARG* and *XRCC1* were found to be associated with protection against acquisition of HBV.
- Our findings suggest that a variety of candidate genetic variants are associated with protection against acquisition of HCV (*CYP1A1, CYP3A4, MBL2* and *TGFB1*) and with increased susceptibility to acquisition of HCV (*CRP, CYP1A2, ITGA2* and *NAT2*).
- Identification of genetic polymorphisms that influence human host susceptibility to HBV and HCV infection may not only help us to better understand the pathogenesis of these diseases, but may also provide a novel rationale for new vaccination and therapeutic strategies.