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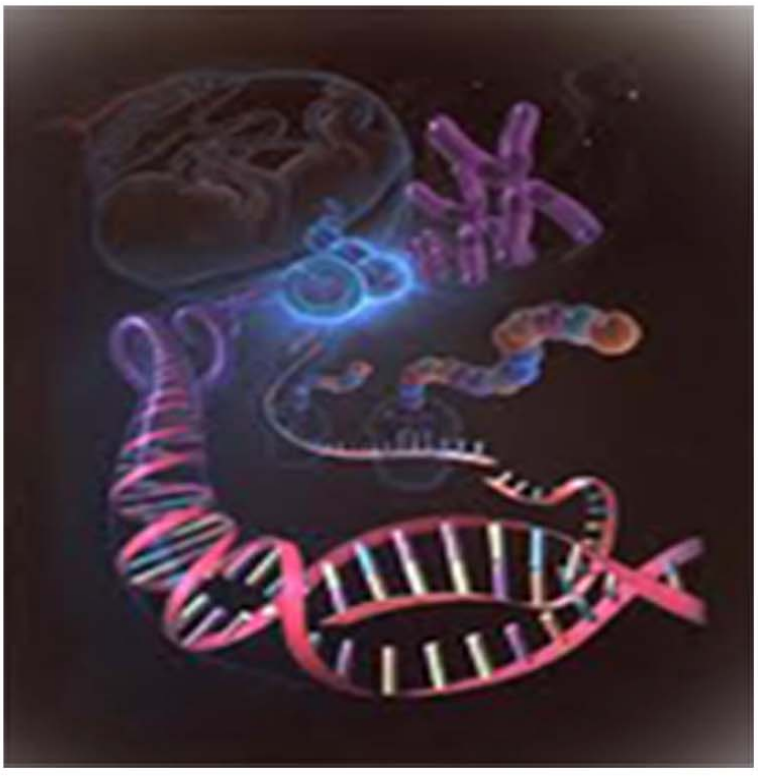

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Review Article

HCV INFECTION AND ITS ASSOCIATION WITH HLA ALLELES

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Host genetic diversity is believed to contribute to the spectrum of clinical outcomes in hepatitis C virus (HCV) infection. The frequencies of HLA class I and class II alleles of HCV infected were reviewed and analyzed with literature available from published literature. The analysis showed that he associations of HLA-A*02 and HLA-DRB1*12 with HCV infection are opposite with different races. HLA-A*03, Cw*05, DRB1*01, DQB1*03 and DQB1*05 are associated with viral clearance while HLA-DRB1*07 and DQB1*02 are risk markers for viral persistence of HCV infection in Midwestern Americans. These results reveal ethnically and geographically different distribution of HLA-genes which are associated with the outcome of HCV infection.

Keywords: HCV, HLA, association

INTRODUCTION

Hepatitis C virus (HCV) is an important blood related pathogen (Villano et al., 1999) as lack of efficient immune responses (Spengler et al., 1996) are involved borne pathogen that is eliminated from the host in the pathogenesis of chronic hepatitis. Further it is approximately 15 percent of acutely infected liver damage in HCV infected patients is probably individuals but persists in the remaining 85 percent is associated with direct cytopathic effects and immune HCV is responsible for a wide spectrum of chronic mediated mechanisms (Mosnier et al., 1993). Though, the exact basis for the liver lesions ranging from minimal to cirrhosis or differential clinical presentation of HCV infection is not Hepatocellular Carcinoma (HCC) and fatal outcome (Tsukuma et al., 1993, Vander Poel et al., 1994). Fully understood, viral load and genotype (Yuki et al., 1994) have been both virus-related factors such as viral heterogeneity reported to influence the prognosis. The observation of replicative activity (Silini et al., 1995) and the host determinants such different clinical presentations despite the same source of infection led to the recognition of the importance of host genetic factors in disease manifestations. In an Irish Cohort, of the 704 women infected with HCV from contaminated anti-D immuno globulin, 390 (55%) became persistently infected. MHC class I and class II antigens are central to the host immune response and thus are ideal

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candidate genes to investigate for associations with HCV. Class I and Class II HLA are encoded by the most polymorphic genes that present antigens to CD8+ cytotoxic T cells and CD4+ helper T cells respectively. Polymorphisms in binding regions of these molecules determine antigenic specificities and the strength of the immune response to a given pathogen. Moreover during cellular immune response, HLA class I molecules may present HCV epitopes to cytotoxic T cells, resulting in a protective immune response (Table 1).

The human leukocyte antigen is a crucial genetic factor that initiates and regulates immune

Table 1: HLA-Class I Allele Frequencies of HCV Infected Subjects

Allele	Chronic(%) 2n = 112	Clearance (%) 2n = 98	Odds Ratio	95% CI	p-value
A*01	15.2	9.18	2.05	0.79–5.32	0.14
A*02	26.8	26	1.04	0.48–2.24	0.92
Caucasian	30.3	17.4	**2.07**	0.82–5.21	0.12
non-Cauc	21.7	32.7	**0.57**	0.23–1.42	0.23
A*03*	9.82	16.7	0.54	0.24–1.20	0.14
A*11	3.57	6.25	0.55	0.15–2.08	0.38
A*23	1.79	4.17	0.42	0.07–2.38	0.33
A*24	10.7	15	0.94	0.37–2.38	0.9
A*25	1.79	1.25	1.78	0.16–20.2	0.64
A*29	5.34	1.25	0.18	0.02–1.50	0.12
A*30	7.14	3.12	2.56	0.64–10.2	0.19
A*31	3.57	5.21	0.68	0.17–2.68	0.58
A*32	1.79	4.17	0.42	0.07–2.38	0.33
A*33	2.68	1.04	2.71	0.27–27.0	0.39
A*68	2.68	4.17	0.64	0.14–2.08	2.99
A*74	2.68	1.04	0.37	0.04–3.66	0.62
Cw*01	1.79	4.08	0.57	0.09–3.55	0.55
Cw*02	9.84	7.16	1.47	0.52–4.13	0.47
Cw*03	10.7	9.18	1.21	0.46–3.18	0.7
Cw*04	16.9	13.2	1.31	0.56–3.06	0.53
Cw*05	0.89	7.16	**0.12**	**0.01–0.97**	**0.03**
Cw*06	8.94	9.18	1.11	0.40–3.09	0.84
Cw*07	28.6	28.6	0.88	0.41–1.91	0.75
Cw*08	4.46	3.06	1.18	0.25–5.55	0.84
Cw*12	3.58	6.12	0.55	0.15–2.08	0.38
Cw*15	3.58	2.05	1.81	0.32–10.3	0.51
Cw*16	7.15	8.16	0.85	0.29–2.48	0.77

Note: * A*03 is protective for non-Caucasians, OR = 0.20, 95% CI = 0.04–1.01, P = 0.04

responses by presenting foreign or self-antigens to T lymphocytes. Certain HLA alleles have been shown to influence the outcome of chronic HCV infections (Irshad et al., 1995, Jain et al., 2003). Various HLA alleles have been linked with either persistence or clearance of the virus. Several studies have aimed to identify the involvement of HLA with different outcomes of HCV infection, but the results have not been consistent. Moreover literature review revealed that the prevalence of HCV infection is significantly low in Indian population (Anuradha et al., 2009, Jain et al., 2003, Chowdhary et al., 1999, Irshad et al., 1995).

DISCUSSION

Indian Scenario

Data on HLA association with HCV infection have been reported from western India. It has been reported that among the HLA A locus, the frequencies of HLA A*03, A*26, A*32 and A*66 alleles increased, the increaes of the first two alleles were highly significant. Similarly, A*11, A*24 and A*33 alleles decreased among patients compared to controls. Among the HLA B locus, the frequencies of alleles HLA B*08, B*15, B*55 and B*57 increased, increase in the allele frequency of B*15 was highly significant. Similarly, allele B*40 decreased. Among the HLA C locus, the frequencies of HLA Cw*01, Cw*08, CW*16 and Cw*18 alleles increased while Cw*06 decreased in HCV infected individuals compared to controls. Further among the class II alleles HLA DRb1*03, DRb1*12, DRB1*16 and DQB1*03 alleles significantly increased while DRB1*01 and DQB1*05 decreased through not significantly. HLA II locus haplotype analysis revealed that HLA haplotype DRB1*11DQB1*03 was significantly associated among the patients (Table 2). This haplotype was derived by direct counting.

One of the striking features of HCV infection is the very high rate of development of chronicity.

Approximately 15 percent of infected patients successfully eliminate the virus, while others develop chronic infection with a wide spectrum of disease. Some will remain asymptomatic whereas others may have a more severe course leading to cirrhosis or hepatocellular carcinoma. There are evidences that immune mechanisms contribute to control the HCV infection. In the host immune reaction against viral infections HLA alleles play vital role in modulating the immune responses. Hence, this study was designed to examine the frequencies of HLA class I and class II genotype profiles in HCV infected western Indian individuals. The major findings of the present study were a significant increase among the allele frequencies of HLA A*03, A*32, HLA B*15, B*55, Cw*16, Cw*18, DRB1*03 and DQB1*03 in the western Indian patients population when compared with the controls from the same population (Anuradha *et al*., 2009) and HLA II-locus haplotype DRB1*11-DQB1*03 was significantly increased among HCV infected individuals (Table 2).

Yoon SK et al., (2005) have reported that the frequencies of HLA-A3, HLA-B35 and HLA-B46 significantly increased in chronic HCV carriers compared with the controls in the Korean population. In an Egyptian population, Zekri et al., (2005) observed HLA class I and II alleles A28, A29, B14 and DR7 to be significantly encountered in HCV positive than negative cases. An association of HLA B27 with spontaneous HCV clearance has also been reported (Newmann-haefelin et al., 2006). Thio etal (1994) have reported an association of Cw*0102 with HCV clearance in Caucasians and of A*2301 and Cw*04 with HCV persistence in both African-

Table 2: HLA-Class II Allele Frequencies of HCV Infected Subjects

Allele	Chronic (%) (2n = 112)	Clearance (%) (2n = 98)	Odds Ratio	95% CI	*p*-Value
DRB1*01	6.25	14.6	0.37	0.12 – 1.08	0.07
Caucasian	7.58	19.6	0.27	0.13 – 1.00	0.05
DRB1*03	14.3	10.4	1.56	0.63 – 3.86	0.34
DRB1*04	13.4	18.7	0.83	0.35 – 1.98	0.68
DRB1*07	17	8.35	2.42	0.95 – 6.23	0.07
DRB1*09	1.6	2.08	0.87	0.12 – 6.24	0.89
DRB1*11	10.7	12.5	0.84	0.34 – 2.09	0.71
DRB1*12	4.46	6.25	0.7	0.20 – 2.46	0.58
DRB1*13	16.1	9.38	1.62	0.64 – 4.12	0.31
DRB1*14	3.7	8.35	0.46	0.12 – 1.68	0.24
DRB1*15	9.82	6.25	1.75	0.60 – 5.15	0.31
DRB1*16	2.67	2.08	1.33	0.21 – 8.31	0.76
DQB1*02	25.9	16.3	1.79	0.91 – 3.54	0.09
Caucasian	34.8	15.2	2.98	1.15 – 7.71	0.02
DQB1*03	28.6	40.8	0.39	0.18 – 0.92	0.02
non-Cauc	23.9	44.2	0.2	0.06 – 0.67	0.01
DQB1*04	5.4	2.1	4.24	0.76 – 23.6	0.1
DQB1*05	10.7	21.4	0.42	0.18 – 1.01	0.05
Caucasian	9.1	23.9	0.23	0.07 – 0.82	0.02
DRB1*06	29.4	19.4	1.72	0.79 – 3.76	0.17

Note: Only alleles with more than 1.0% frequency in both comparison groups are shown. non-Cauc: non-Caucasian.

Table 3: Protective and Susceptibility HLA-Alleles in Different Races

	Caucasians		Non-Caucasian Americans*		
Allele	**European**	**American**	**AA**	**HL**	**Reference**
Protective					
A*02			Chicago	Chicago	Koziel, 2005
A*03	Irish**		Chicago	Chicago	Kenny-Walsh, 1999; and Jane H Wang *et al.*, 2009
A*11		Baltimore	Baltimore		17
B*27	Irish				16
B*57		Baltimore	Baltimore		17
Cw*01	Irish	Baltimore			16, 17
Cw*05	Chicago	Chicago	Chicago		12
DRB1*01	Irish	Baltimore, Chicago			1216,26

Table 3 (Cont.)

	Caucasians		Non-Caucasian Americans*		
Allele	**European**	**American**	**AA**	**HL**	**Reference**
DRB1*11	British, Italian	Philadelphia			09, 20, 23
DRB1*12			Chicago	Chicago	23
DQB1*03	British	Philadelphia Chicago	Baltimore Chicago		09, 23,27 12
DQB1*05	Irish	Baltimore, Chicago			16, 23, 27
Susceptibility					
A*02		Chicago			
A*23				Baltimore	26
Cw*04		Baltimore	Baltimore		26
DRB1*03	Irish, German	Baltimore			10, 20, 24
DRB1*07	British	Chicago			12,23,
DRB1*12		Chicago			12
DQB1*02	Irish	Baltimore, Chicago			12,20, 26,

Note: * All Americans are injection drug users; AA: African American; HL: Hispanic Latino American. **: Irish females. Sample size (n): Irish: 227; British: 250; Baltimore:548/675; Chicago: 105; Philadelphia: 93; German: 75; and Italian: 73.(Adapted from ref12)

Table 4: HLA Distribution in Anti-HCV Positive Individuals and Controls from Maharashtra, India

HLA	Anti-HCVpositives	Controls						
	n =43	n =67						
	AF (%)	AF (%)	OR	Ki2	EF	PF	*p*-Value	
A*03	47.91	5.22	16.69	12.12	0.44		7.90E-12	**
A*11	2.08	11.94	0.15			0.1	0.04	
A*24	6.25	23.88	0.21			0.18	0.007	
A*26	2.08	0.74	2.82		0.01			
A*31	4.16	6.71	0.6					
A*32	22.91	0	1474		0.21		1.80E-08	**
A*33	2.08	8.95	0.21			0.06		
A*66	6.25	1.49	4.4		0.04			
A*68	6.25	4.47	1.42					
B*07	10.41	9.7	1.08					
B*08	6.25	2.23	2.91		0.03			
B*15	43.75	5.22	14.11	10.42	0.39		2.18E-10	**
B*27	4.16	2.98	1.41					
B*40	8.33	23.88	0.28			0.17	0.02	
B*44	8.33	17.16	0.43			0.09		

Table 4 (Cont.)

HLA	Anti-HCVpositives	Controls						
	n =43	n =67						
	AF (%)	AF (%)	OR	Ki2	EF	PF	*p*-Value	
B*51	8.33	4.47	1.93					
B*55	8.33	0.74	12.09	1.81	0.07		0.005	
B*57	2.08	0	134		0.01		0.09	
Cw*01	6.25	1.49	4.4		0.04		0.08	
Cw*02	4.16	3.73	1.12					
Cw*03	4.16	10.44	0.37					
Cw*04	16.66	16.41	1.01					
Cw*06	6.25	19.4	0.27				0.03	
Cw*07	12.5	22.38	0.49					
Cw*08	2.08	0	134		0.01		0.09	
Cw*12	8.33	5.22	1.64					
Cw*14	2.08	2.98	0.69					
Cw*15	14.58	12.68	1.17					
Cw*16	14.58	2.23	7.45		0.12		0.001	
Cw*18	6.25	0	402		0.05		0.003	
	n =39	n =113						
DRB1*01	2.27	7.96	0.26					
DRB1*03	11.36	3.09	4.01		0.08		0.01	
DRB1*07	13.63	13.27	1.03					
DRB1*08	2.27	2.65	0.85					
DRB1*11	20.45	11.94	1.7					
DRB1*12	4.54	0.88	5.3		0.03		0.06	
DRB1*13	2.27	1.32	1.72					
DRB1*15	18.18	10.61	1.87					
DRB1*16	9.09	3.09	3.12		0.06		0.06	
DQB1*02	15.9	15.04	1.06					
DQB1*03	34.09	14.6	3.02		0.22		0.001	
DQB1*05	6.81	8.84	0.75			0.02		
DQB1*06	38.63	26.1	1.78					

Americans and Caucasians (Table 3). In Irish population McKiernan et al(2004) have observed haplotypes A*03B*07-DRB1*15-DQB1*06 and A*02-B27-Cw*01 DRB1*0101-DQB1*0501 to be associated with viral clearance.

We observed the allele A*32 among HCV antibody positive individuals from western India. An increased frequency of haplotype HLA A*11-Cw *04 in viraemic HCV patients was reported in a white population in Ireland22. An association of

B*15 allele with HCV infection was observed in our study. In a European population, Romero-Gomez et al., (2003) have reported the association of HLA-B*44 and sustained HCV response to ribavirin/interferon combination therapy. Among Irish population, (McKierman et al., 2004) have reported increase frequency of B*08 and B*54 in those with chronic HCV infection when compared with those who cleared the infection. DRB1*08 has been reported to be associated with clearance of circulating HCV whereas DRB1*15 appears to predispose to progression of liver disease in Tunisian patients (Ksiaa et al., 2007). It is interesting to note that among western Indians, the frequency of HLA DQB1*03 was higher in anti-HCV antibody positives than in controls, suggesting that the haplotype DRB1*11-DQB1*03 was generated because of the strong linkage disequilibrium of DRB1*11 with DQB1*03 and may or may not be related to the susceptibility to HCV infection (Table 4). Earlier HLA DRB1*03-DQB1*03 haplotype association in western Indian systemic lupus erythromotosis (SLE) patients have been reported due to linkage disequilibrium (Shankarkumar et al., 2003). A trend with DRB1*11 alleles and less severe disease has already been reported (Alric et al 1997). Two studies from United Kingdom have reported higher frequency of DRB1*04, DQA1*03, DQB1*0301 to be associated with resistance to HCV infection (Thurz et al., 1999, Cursino-Santos et al., 2007). As found in our study, higher frequencies of DQB1*0301 and DRB1*1101 were also reported in patients with transient infection in a white population (Alric et al., 1997). The association of viral clearance with two alleles DRB1*01 and DQB1*03 was recently reported in a Brazilian population (Yu et al., 2008). DRB1*1101-DQB1*0301 haplotype seems to be associated with low hepatitis activity in a Chinese population Yu et al., (2008) and Harris et al., (2008) confirmed the previously reported associations between HCV clearance and two HLA types, i.e. DQB1*03 and DRB1*11. Strikingly, these associations were identified only among Caucasian, but not among African American patients.

CONCLUSION

Studies shows that the significant prevalence of haplotype HLA DRB*11-DQB1*03 in HCV antibody positive individuals, and an increased frequency of the haplotype DRB1*11DQB1*03 in HCV antibody positive Indian population may have clinical significance (Anuradha et al., 2009). HLA association with the hepatitis C infection varies in relation to the ethnicity of the population studied. Nevertheless, differences in antigen frequency of selected HLA class I and class II alleles. Moreover, this observation along with the livelihood of acquiring HIV-1 or HIV-2 infection due to high risk behavior could make the situation worse in the Indian context.

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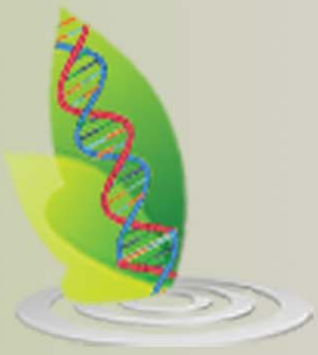

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