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Association of HLA Class II Alleles with Outcome of Hepatitis C Virus Infection: A Systematic Review and Meta-Analysis

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Abstract

Context: Hepatitis C Virus (HCV) infection is a major cause of chronic cirrhosis and hepatocellular carcinoma. Approximately 30% of infected persons with HCV spontaneously clear the viral infection; but, some of the remaining patients develop chronic HCV. Studies show that HLA molecules play an important role in the outcome of HCV infection by influencing the efficiency of the antiviral immune response to HCV infection. It is now known that polymorphisms in HLA loci are associated with HCV susceptibility or clearance. The purpose of the present study was to systematically review the studies that reported the association of HLA class II alleles (HLA-DQ and HLA-DR) with the outcome of HCV infection.

Evidence Acquisition: Studies were identified by searching electronic databases, including PubMed and Scopus. A total of 12,265 relevant studies were identified by the electronic search, of which a total of 19 eligible papers were identified that were meta-analyzed for the association between HLA class II alleles and the outcome of HCV infection.

Results: Subjects carrying HLA-DQB1*0301, HLA-DQB1*0501, HLA-DRB1*1303, HLA-DRB1*1201, HLA-DRB1*0401, HLA-DRB1*0101, and HLA-DRB1*1101 alleles were significantly associated with higher spontaneous clearance of HCV infection.

Conclusions: The data from the current study confirm that several polymorphisms in HLA-DQ and HLA-DR loci are correlated with the clearance of HCV infection. Identifying these polymorphisms may contribute to a better understanding of immune mechanisms of HCV clearance or persistence.

Keywords: Hepatitis C, Human Leukocyte Antigen, Polymorphism, Spontaneous Clearance

1. Context

Hepatitis C virus (HCV) infection is one of the major public health concerns and a major cause of chronic cirrhosis and hepatocellular carcinoma (HCC) in the world (1). Approximately 30% of infected patients spontaneously clear the virus from their bodies, although the majority of the patients develop a chronic infection that can lead to cirrhosis and HCC (2).

Interaction between HCV and immune responses of the host plays an important role in the outcome of HCV infection, although the precise mechanisms underlying the spontaneous viral clearance or development of chronic HCV infection are not fully understood (3). Human leukocyte antigen class-II (HLA-II) is believed to play an important role in immune responses by presenting HCV antigens to CD4 + T cells. These molecules have different abilities to present viral antigens to CD4 + T cells. It has been proposed that diversity in HLA class II alleles may be involved in susceptibility or resistance to HCV infection (4, 5).

Many studies have shown that HLA class II gene polymorphisms may influence HCV infection. Studies of HLA gene polymorphisms and their associations with HCV outcome among various ethnic populations have had conflicting results. For example, the DRB1*0301 allele was associated with persistent HCV infection among German and Thai patients, whereas it was associated with HCV clearance in European and Korean people. The DQB1*0201 allele was associated with HCV clearance in Korean patients, while it was associated with persistent HCV infection in Thai patients (6). Therefore, we performed the present meta-analysis to derive a more precise estimation of the relationship between HLA class II alleles (HLA- DQ and HLA-

DR) and the outcome of HCV infection.

2. Evidence Acquisition

2.1. Search Strategy

We searched databases (PubMed and Scopus) without timeline limits for English-language articles regarding HLA class II gene polymorphisms and their associations with HCV outcome. Our last search was conducted on May 15, 2021. In the present study for including related studies, we used various combinations of the following keywords: (1) "human leukocyte antigen", (2) HLA, (3) "hepatitis C virus", (4) "hepatitis C", (5) HCV, and (6) spontaneous clearance.

2.2. Inclusion and Exclusion Criteria

Reports were regarded as qualified for inclusion if they met the following criteria: Reports with the full text available in the English language, reports with a proper study design such as case-control and cohort studies, reports that provided clear data about HLA class II gene polymorphisms, and their associations with the outcome of HCV infection, reports using high-resolution molecular typing (four-digit HLA typing) method for the HLA class II genes, and studies that reported the frequencies of HLA-DRB1, HLA-DQA1, and HLA-DQB1 alleles in HCV-persistent infection and spontaneous clearance groups. Studies were excluded if they failed to present the data and results clearly and used low-resolution molecular typing (two-digit level) for HLA class II alleles. Furthermore, review articles, case reports, and case series were excluded from the assessment.

2.3. Data Extraction

In the current meta-analysis, two researchers (FS and AG) evaluated the quality of papers to select eligible studies. Following data were extracted from the included studies: The first author's name, year of publication, sample size, frequency of HLA class II alleles in spontaneous HCV clearance groups, and HCV-persistent infection groups. The analysis was performed as per the preferred reporting items for systematic reviews and meta-analysis.

2.4. Quality Assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS). The score range of NOS is from 0 to 9 (7). If the NOS score of a study is $\geq$ 6, it can be considered high quality (8, 9).

2.5. Statistical Analysis

In this meta-analysis, we pooled the outcome estimate using Peto's method with a 95% Confidence Interval (CI). To assess the heterogeneity of the included studies, we used the Q test and I-squared statistic. We also used funnel plots to assess the publication bias. Publication bias was not assessed if the number of studies was < 10. The statistical analyses were performed using Stata software, version 11, and IBM SPSS statistics, version 22.

3. Results

3.1. Search Results and Study Selection

The paper selection process is illustrated in Figure 1. A total of 12,265 documents potentially related to the study objectives were identified through database searching, of which 2,757 papers were considered for the title and abstract screening after duplicate papers were excluded. Next, 2,659 documents were excluded based on title and abstract screening, and 98 articles remained. After the full-text screening, a total of 19 documents were found as eligible papers that evaluated the associations of HLA-class II genetic polymorphisms with HCV clearance. The included studies in this meta-analysis were published between 1997 and 2021. Table 1 lists the characteristics of the eligible and included studies. Regarding the effect of HLA-class II on the clearance of HCV infection, the studies largely evaluated the DQB1*0301 allele (17 studies), DQB1*0201 and DRB1*1101 alleles (14 studies), DQB1*0501, DRB1*0701, and DQB1*0302 alleles (13 studies), DQB1*0602, DQB1*0603, DRB1*0101, and DQB1*0502 alleles (12 studies).

3.2. Meta-Analysis of Association of Class II HLA-DQ Locus Polymorphisms with HCV Clearance

The results of evaluating the class II HLA-DQ locus and its association with HCV clearance showed that subjects carrying HLA-DQB1*0301 and HLA-DQB1*0501 alleles were significantly associated with higher spontaneous HCV clearance (OR = 1.703, 95% CI: 1.464 - 1.981 and OR = 1.264, 95% CI: 1.021 - 1.565, respectively). Conversely, individuals carrying HLA-DQA1*0601, HLA- DQB1*0603, HLA-DQB1*0502, and HLA-DQB1*0201 alleles were associated with a lower probability of spontaneous HCV clearance (OR = 0.286, 95% CI: 0.083 - 0.986, OR = 0.627, 95% CI: 0.438 - 0.899, OR = 0.679, 95% CI: 0.495 - 0.933, and OR = 0.690, 95% CI: 0.578 - 0.824, respectively) (Table 2).

3.3. Meta-Analysis of Association of Class II HLA-DR Locus Polymorphisms with HCV Clearance

Among the studies analyzing the association of class II HLA-DR locus with HCV clearance, the meta-analysis

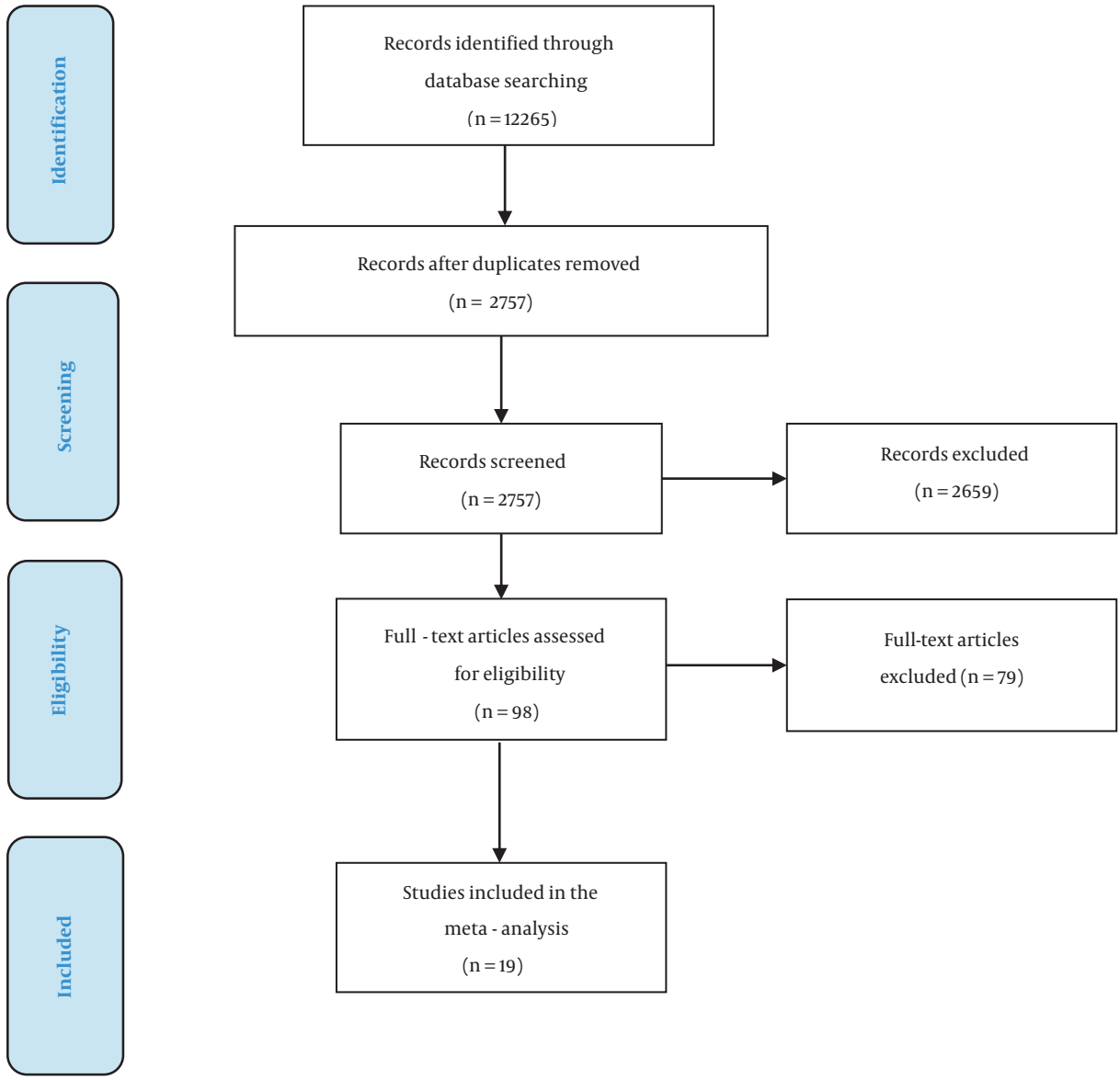

Figure 1. Flowchart of systematic literature search and article selection

identified that HLA-DRB1*1303 (OR = 3.004, 95% CI: 1.078 - 8.376), HLA-DRB1*0401 (OR = 2.124, 95% CI: 1.321 - 3.416), HLA-DRB1*1201 (OR = 1.980, 95% CI: 1.190 - 3.295), HLA-DRB1*1101 (OR = 1.733, 95% CI: 1.387 - 2.166), and HLA-DRB1*0101 alleles (OR = 1.674, 95% CI: 1.281 - 2.189) were significantly associated with higher spontaneous HCV clearance, whereas HLA-DRB1*1301 (OR = 0.435, 95% CI: 0.292 - 0.648), HLA-DRB1*1302 (OR = 0.568, 95% CI: 0.385 - 0.840), HLA-DRB1*0701 (OR = 0.763, 95% CI: 0.602 - 0.966), and HLA-DRB1*0301 alleles (OR = 0.797, 95% CI: 0.638 - 0.995) were associated with lower probability of spontaneous HCV clearance (Table 2).

3.4. Publication Bias Evaluation

In this study, the funnel plot was applied to assess the publication bias, and we did not find any evidence of publication bias (data shown in Appendix). However, the publication bias was not assessed for each HLA class II polymorphism with less than 10 studies.

Table 1. Characteristics of Studies Included in the Meta-analysis

References	Year	Country (Ethnicity)	Spontaneous Clearance [a] (n)	Chronic HCV Infections [b] (n)	HLA Typing	HLA Class II Loci Studied	NOS
Alric (10)	1997	France (European)	25	103	PCR-SSOP	DQB1, DRB1	7
Cramp (11)	1998	United Kingdom (European)	49	55	PCR-SSOP	DQA1, DQB1, DRB1	7
Minton (12)	1998	United Kingdom (European)	35	138	PCR-SSOP	DQB1, DRB1	7
Lechmann (13)	1999	Germany (European)	9	18	PCR-SBT	DRB1	7
Mangia (14)	1999	Italy (European)	35	149	PCR-SSP	DQB1, DRB1	6
Thursz (15)	1999	Mix (European)	85	170	PCR-SSP	DQB1, DRB1	8
Alric (16)	2000	France (European)	63	282	PCR-SSOP	DQB1, DRB1	6
Vejbaesya (17)	2000	Thailand (Asian)	43	57	PCR-SSOP	DQA1, DQB1, DRB1	6
McKiernan (18)	2000	Ireland (European)	95	148	Reverse line probe hybridization	DQB1, DRB1	8
Thi (19)	2001	USA (American)	200	374	PCR-SSP	DQA1, DQB1, DRB1	6
Azocar (20)	2003	USA	40	72	PCR-SSOP	DQB1	6
Spada (21)	2004	Italy (European)	10	24	PCR-SSP	DQB1, DRB1	6
Romero (22)	2009	USA	39	121	PCR-SSPPCR-SSOP	DQB1, DRB1	7
Mangia (23)	2011	Italy (European)	49	68	Reverse line probe hybridization	DQB1, DRB1	7
Mangia (24)	2013	Italy (European)	47	122	Reverse line probe hybridization	DQB1, DRB1	7
Samimi Rad (25)	2015	Iran (Asian)	54	63	PCR-SSP	DQA1, DQB1, DRB1	7
Huang (26)	2016	China (Asian)	231	429	PCR-SBT	DQB1, DRB1	7
El-Bendary (27)	2019	Egypt (African)	108	235	PCR-SBT	DRB1	6
Huang (28)	2019	China (Asian)	59	84	PCR-SBT	DQB1, DRB1	7

Abbreviations: SSP, sequence-specific primers; SSOP, sequence-specific oligonucleotide probe; SBT, sequence-based typing; NOS, Newcastle-Ottawa Scale.
[a] Anti-HCV positive and HCV-RNA negative
[b] Anti-HCV and HCV-RNA positive

4. Conclusions

The HCV infection is considered a multifactorial disease influenced by environmental and host factors. Host factors such as the innate and adaptive immune response play a crucial role in the outcomes of HCV infection (6, 29). It has been proposed that HLA molecules are the host factors that may influence the efficiency of the antiviral immune response to HCV infection. Various studies have confirmed that polymorphisms in HLA loci are associated with the outcome of HCV infection (6). Identifying these polymorphisms may help better understand the immune mechanisms of HCV clearance or persistence. The objective of this meta-analysis was to establish the updated information about the association of HLA class II alleles with clearance or persistence of HCV infection. The results showed that subjects carrying HLA-DQB1*0301, HLA-DQB1*0501, HLA-DRB1*1303, HLA-DRB1*1201, HLA-DRB1*0401, HLA-DRB1*0101, and HLA- DRB1*1101 alleles were significantly associated with higher spontaneous HCV clearance. These findings are almost similar to a previous systematic review conducted by Gauthiez et al. that reported HLA-DRB1*1101, HLA-DRB1*1201, HLA-DRB1*0101, and HLA-DQB1*0301 alleles were associated with HCV clearance (30). For HLA-DQB1*0501, HLA-DQB1*0603, and HLA-DRB1*1301 alleles, in contrast to our study, Gauthiez et al. reported a lack of association with HCV clearance (30). These inconsistent results may be due to the differences in the number of studies and the number of populations included in the meta-analysis. For example, for the HLA-DRB1*1301 polymorphism, we included four additional investigations in our meta-analysis compared to the meta-analysis published by Gauthiez et al. in 2017 (30). In addition, in 2005, a meta-analysis evaluated the association of HLA-DQB1*0301 and HLA-DRB1*1101 alleles with the outcome of HCV infection and reported that subjects carrying HLA-DQB1*0301 and HLA-DRB1*1101 alleles showed a reduced risk of developing

Table 2. Meta-Analysis of Association of Class II HLA Alleles With HCV Spontaneous Clearance

HLA Alleles	Number of Studies	Spontaneous Clearance		Chronic HCV Infections		Odds Ratio) 95% CI)	P Value	I^2 Value (%)	Heterogeneity P Value
		Number	Positive	Number	Positive				
DQA1*0101	4	346	64	549	99	1.032 (0.729 - 1.461)	0.859	45.6	0.138
DQA1*0102	4	346	65	549	116	0.863 (0.615 - 1.212)	0.442	0	0.566
DQA1*0103	4	346	18	549	40	0.698 (0.394 - 1.239)	0.265	0	0.703
DQA1*0201	4	346	68	549	93	1.199 (0.848 - 1.696)	0.326	74.5	0.008
DQA1*0401	3	146	8	175	20	0.449 (0.192 - 1.053)	0.074	0	0.681
DQA1*0501	4	346	99	549	140	1.171 (0.866 - 1.584)	0.314	52.9	0.095
DQA1*0601	3	292	3	486	17	0.286 (0.083 - 0.986)	0.036	55.4	0.106
DQB1*0201	14	1052	219	2041	563	0.690 (0.578 - 0.824)	0.000	52.7	0.011
DQB1*0202	4	415	36	717	69	0.892 (0.585 - 1.361)	0.671	71.1	0.016
DQB1*0301	17	1164	416	2421	596	1.703 (1.464 - 1.981)	0.000	57.5	0.002
DQB1*0302	13	920	84	1829	167	1.000 (0.760 - 1.317)	1.000	11.9	0.326
DQB1*0303	10	786	67	1474	109	1.167 (0.850 - 1.603)	0.365	0	0.897
DQB1*0401	5	245	10	331	12	1.131 (0.481 - 2.662)	0.828	0	0.726
DQB1*0402	7	436	19	860	39	0.959 (0.547 - 1.681)	1.000	0	0.917
DQB1*0501	13	776	171	1538	281	1.264 (1.021 - 1.565)	0.035	52.6	0.013
DQB1*0502	12	885	57	1608	148	0.679 (0.495 - 0.933)	0.018	0	0.887
DQB1*0503	5	333	12	612	30	0.725 (0.366 - 1.436)	0.411	5.4	0.376
DQB1*0601	10	790	45	1365	72	1.085 (0.739 - 1.591)	0.694	0	0.884
DQB1*0602	12	953	112	1885	242	0.904 (0.712 - 1.148)	0.434	31.2	0.142
DQB1*0603	12	762	42	1528	130	0.627 (0.438 - 0.899)	0.011	0	0.760
DQB1*0604	10	624	29	1323	51	1.216 (0.763 - 1.937)	0.463	0	0.824
DQB1*0605	4	157	2	275	6	0.578 (0.115 - 2.901)	0.716	0	0.983
DRB1*0101	12	866	109	1667	132	1.674 (1.281 - 2.189)	0.000	60.4	0.002
DRB1*0102	5	342	10	664	19	1.023 (0.470 - 2.224)	1.000	0	1.000
DRB1*0103	2	144	8	203	12	0.936 (0.373 - 2.352)	1.000	0	0.914
DRB1*0301	11	995	129	1924	303	0.797 (0.638 - 0.995)	0.048	41.8	0.063
DRB1*0304	2	104	1	166	1	1.602 (0.099 - 25.892)	1.000	0	0.356
DRB1*0401	5	309	41	521	35	2.124 (1.321 - 3.416)	0.003	56.2	0.058
DRB1*0403	3	127	3	274	5	1.302 (0.306 - 5.533)	0.712	0	0.616
DRB1*0404	2	138	17	205	13	2.075 (0.973 - 4.424)	0.078	0	0.802
DRB1*0405	5	490	29	873	49	1.058 (0.659 - 1.698)	0.809	59.7	0.042
DRB1*0406	2	78	1	206	7	0.369 (0.045 - 3.051)	0.453	0	0.714
DRB1*0701	13	965	109	1929	276	0.763 (0.602 - 0.966)	0.027	52.3	0.014
DRB1*0801	2	104	1	118	3	0.372 (0.038 - 3.634)	0.625	0	0.684
DRB1*0803	2	274	21	486	33	1.139 (0.645 - 2.011)	0.661	0	0.770
DRB1*0901	7	744	52	1297	81	1.128 (0.787 - 1.618)	0.515	0	0.997
DRB1*1001	8	547	12	1019	22	1.016 (0.499 - 2.070)	1.000	0	0.896
DRB1*1101	14	1042	158	2150	201	1.733 (1.387 - 2.166)	0.000	45.4	0.033
DRB1*1102	2	209	7	392	10	1.324 (0.496 - 3.530)	0.610	10.2	0.291
DRB1*1103	2	235	1	523	5	0.443 (0.051 - 3.811)	0.672	0	0.946
DRB1*1104	6	384	30	794	63	0.983 (0.625 - 1.547)	1.000	56.5	0.042
DRB1*1201	8	430	29	965	34	1.980 (1.190 - 3.295)	0.011	27	0.213
DRB1*1202	2	274	29	486	51	1.010 (0.623 - 1.635)	1.000	0	0.429
DRB1*1301	10	560	32	1162	142	0.435 (0.292 - 0.648)	0.000	24.9	0.214
DRB1*1302	10	560	35	1162	122	0.568 (0.385 - 0.840)	0.004	16.5	0.291
DRB1*1303	5	245	8	630	7	3.004 (1.078 - 8.376)	0.040	0	0.971
DRB1*1305	2	52	4	75	6	0.958 (0.257 - 3.579)	1.000	66.7	0.083
DRB1*1401	7	412	15	966	47	0.739 (0.408 - 1.337)	0.394	0	0.712
DRB1*1501	8	582	65	1117	154	0.786 (0.577 - 1.071)	0.147	0	0.595
DRB1*1502	6	494	7	967	17	0.803 (0.331 - 1.950)	0.828	0	0.531
DRB1*1601	7	397	17	855	22	1.694 (0.889 - 3.227)	0.116	0	0.837
DRB1*1602	3	111	25	159	36	0.993 (0.556 - 1.774)	1.000	0	0.404

chronic HCV infection (31), which is similar to this study and Gauthiez et al.'s meta-analysis (30). The results of our study also are in agreement with the results of studies by McKiernan et al. (18) and Thio et al. (19) that found the HLA-DQB1*0501 allele was associated with HCV clearance; however, in contrast to our study, Romero et al. reported that this allele was associated with persistent HCV infection (22). These contradictory results may be due to sample size and ethnic differences. It has been proposed that both viral genotype and host ethnicity can influence immunity against HCV infection. The relationship between HCV clearance and certain HLA alleles appears to be racially and geographically specific (19, 32). Therefore, well-designed studies in multiple regions are needed to confirm these results.

Some limitations exist in the present study that should be noted. First, the sample size in some of the included studies was small; therefore, further studies are needed to confirm the results. Second, the studies included in the present meta-analysis varied in the HLA typing technique, which may have affected the obtained results of this study. Third, some data were not included in the analysis since their original language was not English. Finally, some HLA class II polymorphisms were assessed in only two or three studies; therefore, more studies are needed to determine the association of HLA class II alleles with HCV outcome.

Taken together, the present meta-analysis provides detailed data on the association of HLA class II polymorphisms with HCV outcome. In the current meta-analysis, HLA-DQB1*0301, HLA-DQB1*0501, HLA- DRB1*1303, HLA-DRB1*1201, HLA-DRB1*0401, HLA-DRB1*1101, and HLA-DRB1*0101 alleles were significantly associated with higher spontaneous HCV clearance, whereas HLA-DQA1*0601, HLA-DQB1*0603, HLA-DQB1*0502, HLA-DQB1*0201, HLA-DRB1*1301, HLA-DRB1*1302, HLA-DRB1*0701, and HLA-DRB1*0301 alleles were associated with lower probability of spontaneous HCV clearance. Identifying an association between HLA class II polymorphisms and HCV outcome may open new insights to better understand the immune mechanisms of HCV clearance or persistence.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design, F. S; Analysis and interpretation of data, M. G-F. and A. G; Drafting of the manuscript, H. G-Z.; Critical revision of the manuscript for important intellectual content, F. S. and A. G; Statistical analysis, M. G-F.

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