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Relationship between *HLA-DP* gene polymorphisms and the risk of hepatocellular carcinoma: a meta-analysis

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ABSTRACT. The association between the *HLA-DP* single nucleotide polymorphisms (SNPs) rs3077 and rs9277535 and hepatocellular carcinoma (HCC) has been reported, but results have been inconclusive and controversial. Therefore, to investigate the relationship between these *HLA-DP* SNPs and HCC susceptibility, a meta-analysis of studies published before January 2014 was carried out using the PubMed and Google Scholar databases. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated for *HLA-DP* alleles, and for co-dominant, dominant, and recessive genotype models of each SNP, based on fixed- or random-effects models. A total of nine studies from six published articles were included. The association study between rs3077 and HCC susceptibility was performed in four independent comparisons that contained 1871 cases with hepatitis B virus (HBV)-related HCC and 3207 carriers with

persistent HBV. Association between rs9277535 and HCC susceptibility was examined in five separate comparisons that contained 2017 cases and 3930 carriers. Our analysis indicated a significant association of rs3077 and rs9277535 with HCC susceptibility, suggesting that rs3077 might act beneficially against HCC susceptibility (A *vs* G: OR = 0.884, 95%CI = 0.803-0.973, P = 0.012; GA *vs* GG: OR = 0.842, 95%CI = 0.733-0.967, P = 0.015; AA+GA *vs* GG: OR = 0.848, 95%CI = 0.744-0.968, P = 0.014), and that rs9277535 might promote HCC susceptibility (AA *vs* GA: OR = 1.202, 95%CI = 1.011-1.428, P = 0.037). This study suggested that *HLA-DP* rs3077 and rs9277535 polymorphisms are associated with HCC susceptibility in the Asian population.

Key words: *HLA-DP*; SNP, Meta-analysis, Hepatocellular carcinoma

INTRODUCTION

Liver cancer is the fifth most frequently diagnosed cancer worldwide but the second most frequent cause of cancer death (Jemal et al., 2011). Hepatocellular carcinoma (HCC) is one of the most common cancers and causes cancer mortality worldwide, especially in East and Southeast Asia and in sub-Saharan Africa (Tsukuma et al., 2005; Yeo et al., 2013). Globally, there are more than 250,000 new cases of HCC and an estimated 500,000-600,000 deaths due to this disease annually (Arzumanyan et al., 2013). Eastern Asia is the geographic area at highest risk of HCC, and China accounts for 55% of all HCC cases worldwide (Jemal et al., 2011). Major risk factors for HCC include chronic infection with the hepatitis B (HBV) or C (HCV) virus, exposure to dietary aflatoxin B1, and cirrhosis of any etiology. HBV infection is particularly important in Asia and other developing countries (Arzumanyan et al., 2013), and HCV infection is particularly important in Western countries and Japan (Sarma et al., 2012).

The mechanisms that determine the development of HCC in chronic HBV infection have yet to be identified. Studies have demonstrated that chronic HBV carriers with a family history of HCC have a two-fold risk for HCC over those without any family history (Yu et al., 2000), which suggested that genetic susceptibility for HBV-related HCC is a strong component of this disease. Furthermore, it is common knowledge that single nucleotide polymorphisms (SNPs) in immune response and tumorigenesis related genes, such as *XPD*, *XRCC1*, *MDR1*, *EGF*, *TGF-beta1*, *TNF-alpha*, *TP53*, and *GSTT1* might affect the host immune response to virus infection as well as provide crucial genetic markers for determining the stages of HCC development (Chen et al., 2012; Guo et al., 2012; Ren et al., 2012; Li et al., 2012, 2013; Thongbai et al., 2013).

HLA-DPs are heterodimeric molecules consisting of alpha and beta chains that are encoded by the *HLA-DPA1* and *-B1* genes. The SNPs rs3077 and rs9277535 of *HLA-DP* have been reported to be associated with the persistence of HBV infection and with spontaneous HBV clearance (Guo et al., 2011; Cheng et al., 2013; Hu et al., 2013). Recently, a relationship between the *HLA-DP* gene and HCC susceptibility has been reported by multiple labs, but the results have been discordant (An et al., 2011; Li et al., 2011; Hu et al., 2012; Chen et al., 2013; Al-Qahtani et al., 2014; Posuwan et al., 2014). Therefore, in order to clarify the role of *HLA-DP* polymorphisms in HCC susceptibility, a systematic review and meta-analysis of published data were carried out in this study.

MATERIAL AND METHODS

Literature search strategy

A systematic literature search was conducted using the databases PubMed (National Center for Biotechnology, National Library of Medicine) and Google Scholar before January 2014 with key words "*HLA-DP*", "Hepatocellular carcinoma" or "HCC" or "liver cancer", "polymorphism" or "SNP", and "rs3077" or "rs9277535". The languages of the reviewed articles were limited to English and Chinese. All searched studies were retrieved and their bibliographies were checked for additional publications.

Inclusion and exclusion criteria

The inclusion criteria in the current meta-analysis were as follows: 1) solid evidence for HBV-related HCC diagnosis; 2) the study was a case-control design; 3) the study aimed to examine the association between the "rs3077" or "rs9277535" polymorphism and susceptibility to HCC; 4) the study provided the available genotype frequencies; and 5) the genotype distribution of the control group must have been fitted against Hardy-Weinberg equilibrium (HWE).

The exclusion criteria in the current meta-analysis were as follows: 1) the study was not a case-control study; 2) no gene frequency distributions of the polymorphic locus/loci were provided.

Data extraction

The following information was extracted from each study and is summarized in Table 1: first author, publication year, country, numbers of cases and controls, minor allele and minor allele frequency, and the genotype numbers of cases and controls for the rs3077 and rs9277535 polymorphisms.

Meta-analysis methods

Statistical manipulations were performed using STATA 11.0 (Stata Corporation, College Station, Texas, USA). The strength of the associations between HCC susceptibility and *HLA-DP* polymorphisms were estimated by odds ratios (ORs) and 95% confidence intervals (CIs). The pooled OR was determined by the Z test and statistical significance was set at $P < 0.05$. All P values were double-sided. The allelic frequencies of rs3077 and rs9277535 from each study were determined using the allele counting method. The data of studies in which combined information from all genotypes was available to compare risks in simple heterozygotes, homozygotes, and recessive and dominant models were also included.

To assess the between-study heterogeneity more precisely, the χ^2-based Cochran's Q-statistic (Davey Smith and Egger, 1997) was used. If a significant Q-statistic ($P > 0.05$) indicated heterogeneity across studies, the random-effects model was used for meta-analysis. Otherwise, the fixed-effects model was used. To quantify the proportion of the total variation due to heterogeneity, the effect of heterogeneity was examined via the Higgins (I^2) test (Higgins et al., 2003).

Evaluation of publication bias

We used funnel plots and Egger's linear regression test to assess potential publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). Funnel plot asymmetry was measured by Egger's linear regression test on the logarithm scale of the ORs. The significance of the intercept was determined by the Student *t*-test and $P < 0.05$ was considered representative of statistical publication bias (Egger et al., 1997).

RESULTS

Studies included in the meta-analysis

After scanning the selected databases, 33 potentially relevant articles were selected, of which 19 were not focused on HCC. After reviewing all full texts ascertained from these publications, nine articles were excluded because two did not mention the association between the SNPs and HCC, six did not provide frequencies of alleles or genotypes, and one article did not mentioned the two SNPs under investigation. Five articles containing information on rs3077 and rs9277535 polymorphisms and HCC susceptibility were identified (An et al., 2011; Li et al., 2011; Hu et al., 2012; Al-Qahtani et al., 2014; Posuwan et al., 2014). The flow diagram of the study selection process is shown in Figure 1.

In this study, a total of four separate comparisons (2 Chinese, 2 non-Chinese) were considered for rs3077, which comprised 1871 cases with HBV-related HCC and 3207 carriers with persistent HBV. A total of five separate comparisons (4 Chinese, 1 non-Chinese) were considered for rs9277535, which comprised 2017 cases with HBV-related HCC and 3930 carriers with persistent HBV. Characteristics of the studies included are summarized in Table 1.

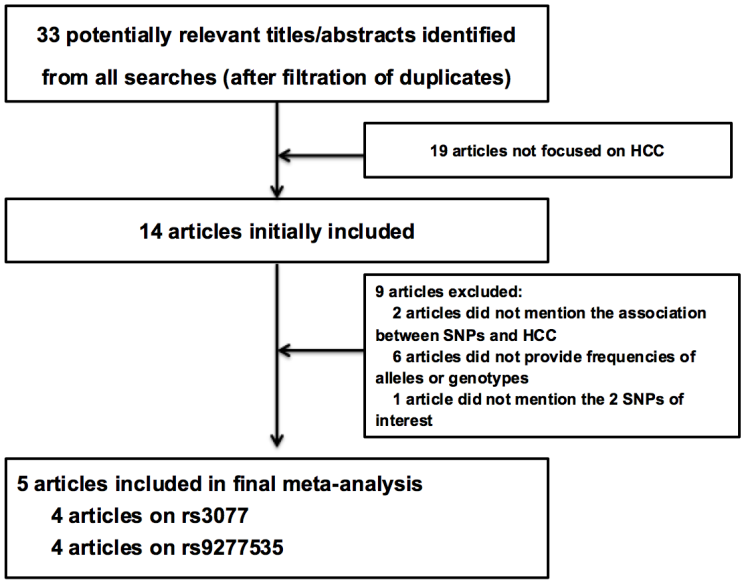

Figure 1. Results of the literature search. HCC = hepatocellular carcinoma; SNPs = single nucleotide polymorphisms.

Table 1. Characteristics of case-control studies included in the meta-analysis.

Study	Country	Number		Polymorphisms evaluated	Minor allele	Minor allele frequency		Genotype[b]						HWE P value
		Patients[a]	Controls			Patients[a]	Controls	Patients[a]			Controls			
								11	12	22	11	12	22	
An et al. (2011)	China	265	961	rs3077	A	0.283	0.296	23	104	138	92	384	485	>0.05
		259	941	rs9277535	A	0.442	0.438	59	111	89	194	437	310	>0.05
Li et al. (2011)	China	340	770	rs9277535	A	0.269	0.258	31	121	188	60	277	433	>0.05
Li et al. (2011)	China	49	198	rs9277535	A	0.347	0.419	7	20	22	33	100	65	>0.05
Hu et al. (2012)	China	1291	1336	rs3077	A	0.258	0.283	99	467	725	107	541	688	>0.05
		1290	1338	rs9277535	A	0.346	0.338	172	548	570	149	607	582	>0.05
Posuwan et al. (2014)	Thailand	230	219	rs3077	A	0.722	0.774	NA	NA	NA	NA	NA	NA	
Al-Qahtani et al. (2014)	Saudi Arabia	85	691	rs3077	A	0.724	0.734	48	27	10	382	251	58	>0.05
		79	683	rs9277535	A	0.715	0.731	42	29	8	372	254	57	>0.05

[a]Individuals positive for HBV infection. [b]"1" stands for the minor allele; "2" stands for the common allele. HWE = Hardy-Weinberg equilibrium; NA = no available genotype information.

Meta-analysis of data included

Outcomes of HCC susceptibility and rs3077

When the two populations were combined together, the overall OR for allele contrast (A *vs* G: OR = 0.884, 95%CI = 0.803-0.973, P = 0.012), heterozygous contrast (GA *vs* GG: OR = 0.842, 95%CI = 0.733-0.967, P = 0.015), and the dominant model (AA+GA *vs* GG: OR = 0.848, 95%CI = 0.744-0.968, P = 0.014) were statistically significant, while the overall ORs for homozygote contrast (AA *vs* GG: OR = 0.862, 95%CI 0.679-1.095, P = 0.225), heterozygous contrast (AA *vs* GA: OR = 1.058, 95%CI = 0.843-1.330, P = 0.626), and the recessive model (AA *vs* GA + GG: OR = 0.962, 95%CI 0.776-1.193, *P* = 0.727) were not statistically significant for HCC susceptibility. Meta-analysis revealed significant association between the rs3077 SNP and HCC susceptibility (A *vs* G: OR = 0.895, 95%CI = 0.805-0.995, P = 0.041; GA *vs* GG: OR = 0.849, 95%CI = 0.738-0.978, P = 0.023; AA+GA *vs* GG: OR = 0.854, 95%CI = 0.747-0.976, P = 0.021) in the Chinese population, but no association between the SNP and HCC susceptibility was discovered in other Asian populations (Saudi Arabian and Thai). The results are shown in Table 2.

Table 2. Main results of the meta-analysis of the association between rs3077 and the risk of HCC.

Polymorphism	Country	Number of studies	Test of association				Test of heterogeneity			Egger's test for publication bias	
			OR	95%CI	Z value	P value	χ^2 value	P value	I^2 (%)	*t*-value	P value
A *vs* G	Overall	4	0.884	0.803-0.973	2.52	0.012	1.47	0.688	0	-0.15	0.895
	China	2	0.895	0.805-0.995	2.05	0.041	0.28	0.598	0	-*	-*
	Other Asian	2	0.831	0.660-1.045	1.58	0.114	0.87	0.351	0	-*	-*
AA *vs* GA	Overall	3	1.058	0.843-1.330	0.49	0.626	0.44	0.803	0	-0.22	0.862
	China	2	1.03	0.797-1.333	0.23	0.819	0.25	0.618	0	-*	-*
	Other Asian	1	1.168	0.710-1.921	0.61	0.541	-*	-*	-*	-*	-*
AA *vs* GG	Overall	3	0.862	0.679-1.095	1.21	0.225	0.22	0.895	0	-1.41	0.392
	China	2	0.878	0.683-1.130	1.01	0.312	0	0.998	0	-*	-*
	Other Asian	1	0.729	0.349-1.520	0.84	0.399	-*	-*	-*	-*	-*
GA *vs* GG	Overall	3	0.842	0.733-0.967	2.43	0.015	1.38	0.502	0	-0.24	0.851
	China	2	0.849	0.738-0.978	2.27	0.023	0.79	0.373	0	-*	-*
	Other Asian	1	0.624	0.286-1.361	1.19	0.236	-*	-*	-*	-*	-*
AA *vs* GA+GG	Overall	3	0.962	0.776-1.193	0.35	0.727	0.22	0.894	0	0.12	0.926
(Recessive model)	China	2	0.939	0.735-1.198	0.51	0.612	0.05	0.831	0	-*	-*
	Other Asian	1	1.049	0.666-1.653	0.21	0.835	-*	-*	-*	-*	-*
AA+GA *vs* GG)	Overall	3	0.848	0.744-0.968	2.45	0.014	0.94	0.624	0	-0.17	0.891
(Dominant model	China	2	0.854	0.747-0.976	2.31	0.021	0.6	0.439	0	-*	-*
	Other Asian	1	0.687	0.337-1.401	1.03	0.302	-*	-*	-*	-*	-*

*Because there were only a few studies with this genotype of rs3077, tests of heterogeneity and/or publication bias could not be calculated. HCC = hepatocellular carcinoma; OR = odds ratio; CI = confidence interval.

Outcomes of HCC susceptibility and rs9277535

When the two populations were combined together, the overall OR for heterozygous contrast (AA *vs* GA: OR = 1.202, 95%CI = 1.011-1.428, P = 0.037) was statistically significant, while the overall ORs for allele contrast (A *vs* G: OR = 1.017, 95%CI = 0.934-1.107, P = 0.7), homozygote contrast (AA *vs* GG: OR 1.103, 95%CI = 0.921-1.321, P = 0.287), heterozygous contrast (GA *vs* GG: OR = 0.917, 95%CI = 0.809-1.038, P = 0.17), and the dominant (AA + GA *vs* GG: OR= 0.961, 95%CI= 0.855-1.080, P = 0.504) and recessive (AA *vs* GA +

GG: OR 0.917, 95%CI 0.809-1.038, P = 0.17) models were not statistically significant for HCC susceptibility. Meta-analysis revealed a significant association between the rs9277535 SNP and HCC susceptibility (AA *vs* GA: OR = 1.234, 95%CI = 1.027-1.483, P = 0.025) in the Chinese population, but no association between the SNP and HCC susceptibility was discovered in other Asian populations (Saudi Arabian). The results are shown in Table 3.

Table 3. Main results of the meta-analysis of the association between rs9277535 and the risk of HCC.

Polymorphism		Number of studies	Test of association				Test of heterogeneity			Egger's test for publication bias	
			OR	95%CI	Z value	P value	χ^2 value	P value	I^2 (%)	*t*-value	P value
A *vs* G	Overall	5	1.017	0.934-1.107	0.39	0.7	2.38	0.666	0	-2.29	0.106
	China	4	1.022	0.937-1.115	0.49	0.622	2.11	0.549	0	-1.76	0.22
	Other Asian	1	0.926	0.642-1.335	0.41	0.68	-*	-*	-*	-*	-*
AA *vs* GA	Overall	5	1.202	1.011-1.428	2.08	0.037	0.9	0.925	0	-2	0.14
	China	4	1.234	1.027-1.483	2.24	0.025	0.23	0.972	0	-4.01	0.057
	Other Asian	1	0.989	0.600-1.629	0.04	0.965	-*	-*	-*	-*	-*
AA *vs* GG	Overall	5	1.103	0.921-1.321	1.06	0.287	2.38	0.667	0	-3.23	0.048
	China	4	1.121	0.931-1.348	1.21	0.227	1.75	0.625	0	-2.14	0.165
	Other Asian	1	0.804	0.359-1.801	0.53	0.597	-*	-*	-*	-*	-*
GA *vs* GG	Overall	5	0.917	0.809-1.038	1.37	0.17	2.17	0.704	0	-1.39	0.258
	China	4	0.919	0.810-1.042	1.32	0.188	2.09	0.554	0	-1.29	0.327
	Other Asian	1	0.813	0.353-1.873	0.49	0.627	-*	-*	-*	-*	-*
AA *vs* GA+GG	Overall	5	1.148	0.976-1.349	1.67	0.095	1.48	0.829	0	-2.71	0.073
(Recessive model)	China	4	1.178	0.992-1.399	1.87	0.062	0.76	0.86	0	-2.75	0.111
	Other Asian	1	0.949	0.595-1.514	0.22	0.826	-*	-*	-*	-*	-*
AA+GA *vs* GG	Overall	5	0.961	0.855-1.080	0.67	0.504	2.7	0.609	0	-1.75	0.178
(Dominant model)	China	4	0.965	0.857-1.086	0.6	0.549	2.51	0.474	0	-1.53	0.265
	Other Asian	1	0.808	0.371-1.762	0.54	0.592	-*	-*	-*	-*	-*

*Because there was only one study with this genotype of rs9277535, tests of heterogeneity and publication bias could not be calculated. HCC = hepatocellular carcinoma; OR = odds ratio; CI = confidence interval.

Study heterogeneity and publication bias

Heterogeneity in the overall study groups was not identified in the meta-analyses (Tables 2 and 3). Egger's test showed that there was no obvious publication bias in this meta-analysis (Tables 2 and 3, Figure 2).

DISCUSSION

HCC is the fifth most common tumor worldwide and the third cause of cancer-related deaths (Parkin et al., 2005). The highest incidence rates of HCC (>20 per 100,000) are in sub-Saharan Africa and Southeast Asia (Nordenstedt et al., 2010). HCC involves complex and heterogeneous malignant tumorigenesis processes, and the pathogenesis of HCC remains incompletely understood, although it is thought to primarily involve host genetic factors such as genetic abnormalities and epigenetic alterations, and environmental factors (Coleman, 2003). Cirrhosis associated with HBV and/or HCV infection and alcohol consumption are the environmental factors that convey the most risk for HCC around the world. Over 80% of HBV-related cirrhosis is the strongest known risk factor for HCC in Asian (Velazquez et al., 2003; Thomas and Zhu, 2005). Some patients without these known risk factors eventually develop HCC as well, suggesting that genetic predisposition might also contribute to the process of hepatocarcinogenesis (Su et al., 2013).

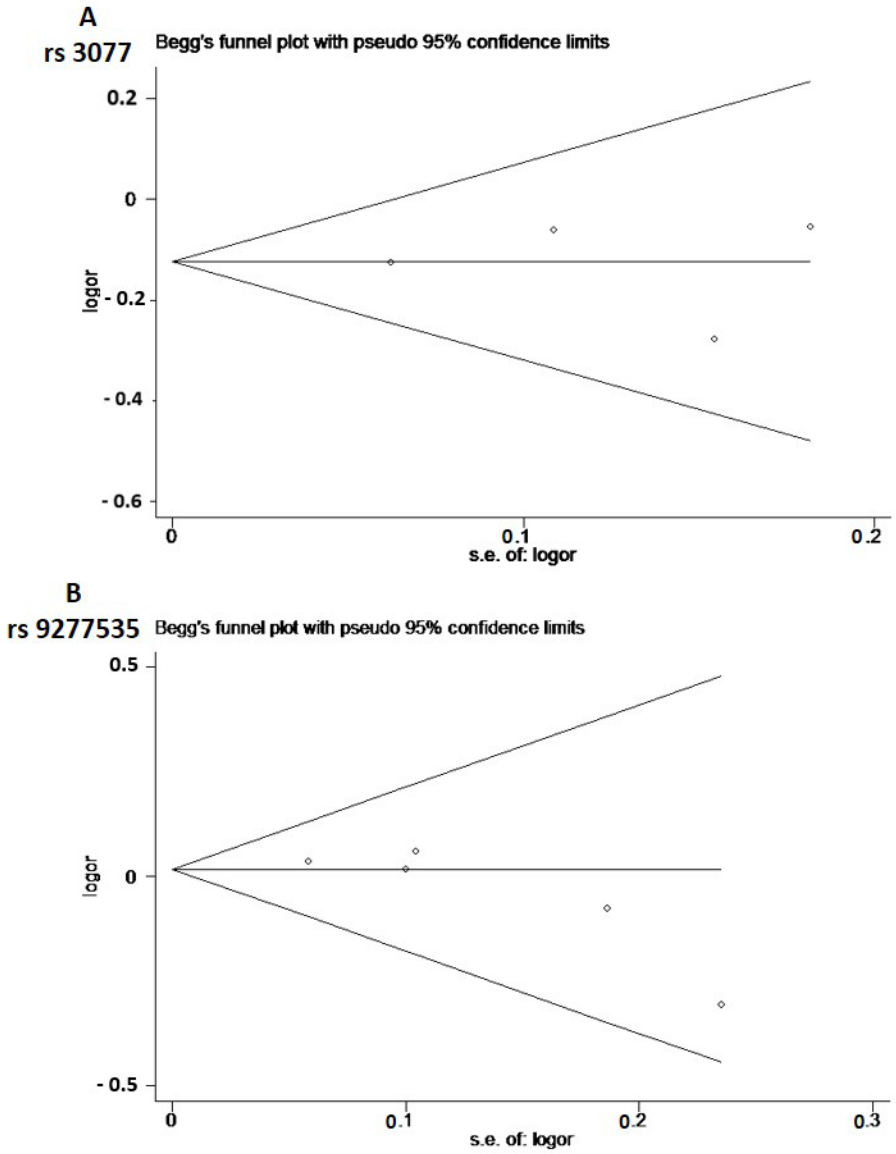

Figure 2. Begg's funnel plots of alleles of rs3077 (**A**) and rs9277535 (**B**) to examine publication bias. Each circle represents a separate study of the indicated association. S.E., standard error.

HLA-DP belongs to the HLA class II group of molecules, which are expressed as cell-surface glycoproteins that bind and present short peptide epitopes to $CD4^+$ T cells. One of the critical roles for the immune response against exposure to HBV is antigen presentation on HLA class II molecules to $CD4^+$ T cells, and on class I molecules to $CD8^+$ cytotoxic T cells (Pieters, 2000). Studies have found that HBV-specific $CD4^+$ T cell responses in patients

with established chronic infections are weak or undetectable, as opposed to the normalized responses in people with resolved infections (Chang et al., 2005). Furthermore, $CD4^+$ T cells were significantly increased in peripheral blood, tumor, and ascites of patients with HCC (Ormandy et al., 2005). These results indicated that HBV-specific, HLA class II-restricted $CD4^+$ T cell responses might be related to HBV-related HCC development. The SNPs rs3077 and rs9277535 are located in the 3' untranslated region of *HLA-DPA1* and *-B1*, respectively. These genes encode the alpha and beta chains of HLA-DP, respectively. It is likely that such polymorphisms might tag HLA-DP alleles that bind relevant HBV epitopes, or tag a variant in a regulatory element that affects HLA-DP stability or expression, affecting HBV antigen presentation by cells and thus the ensuing immune response. Recently, it has been reported that the A alleles of rs3077 and rs9277535 are associated with higher levels of messenger RNA expression of *HLA-DPA1* and *-B1*, respectively, in normal liver tissues. The results suggested that the rs3077 and rs9277535 polymorphisms are important in the regulation of *HLA-DP* expression (O'Brien et al., 2011).

To date, several studies have demonstrated the association of rs3077 and rs9277535 and HCC susceptibility, but these findings remain controversial or inconclusive. To test the hypothesis that a functional association might exist, a systematic review and meta-analysis of published data were carried out in this study. The current systematic review included six eligible studies and was conducted to explore the correlation between the *HLA-DP* rs3077 and rs9277535 polymorphisms and HCC susceptibility.

As demonstrated in the Results section, the HBV-related HCC patients who carried an "A" allele at the allele or genotype level of rs3077 appears to be beneficial. In contrast, compared with the GA genotype, the AA genotype of rs9277535 was suggested to increase HCC risk.

Several factors might contribute to the differences among the published studies. First, genetic heterogeneity might be a reason for the conflicting results. The minor allele of rs3077 in Saudi Arabian and Thai populations and of rs9277535 in the Saudi Arabian populations are the G allele, but in Chinese Han, the minor allele is the A allele. Second, some patient characteristic (e.g., age, gender, family history, environmental factors, cancer stage, and lifestyle) might also potentially contribute to the differences between the studies (Tan et al., 2010), and this meta-analysis was based on unadjusted estimates. Finally, relevant research articles are scarce, which resulted in our sample size in this study not being especially large, which could lead to false-positive results.

In conclusion, our study suggested that the *HLA-DP* rs3077 and rs9277535 polymorphisms are associated with HCC susceptibility in the Asian population, and provide further evidence that genetic factors are important in determining HCC susceptibility. However, the association of *HLA-DP* polymorphisms and HCC susceptibility requires further investigation in larger samples.

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