Association between *RANTES* -403A/G polymorphism and susceptibility to hepatitis B virus infection: A meta-analysis

Xiaxia Zhang[1], Beihong Liu[2], Binbin Wang[2] and Zheng Zeng[1]

[1]Department of Infectious Diseases, Peking University First Hospital, Xicheng, Beijing 100034, China

[2]National Research Institute for Family Planning, Haidian, Beijing 100081, China

Correspondence to: *Zheng Zeng,* ***email***: *zeng@bjmu.edu.cn*
Binbin Wang, ***email***: *wbbahu@163.com*

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ABSTRACT

The relationship between *RANTES* (regulated on activation, normal T cell expressed and secreted) -403A/G polymorphism and susceptibility to hepatitis B virus (HBV) infection were still controversial and unclear. This meta-analysis was performed to resolve this issue. After literature search, eight studies, comprising 2749 cases and 2753 controls, were collected and determined eligible for analysis. No significant association was found between the 403A/G A allele and persistent HBV infection (OR = 1.04, 95% CI = 0.96–1.13, *P* = 0.34). By using subgroup analysis divided by ethnicity, significant association was found between the *RANTES* -403A/G gene polymorphism and susceptibility to HBV infection in the allele model for the Caucasian group (OR = 1.68, 95% CI = 1.38–2.04, *P* < 0.001). In the genotype model, there was also a significant association between -403A/G and the risk of HBV infection (AG versus GG: OR = 1.85, 95% CI = 1.42–2.41, *P* < 0.001; AG+AA versus GG: OR = 1.75, 95% CI = 1.35–2.26, *P* < 0.001) among Caucasians. When using healthy individuals as controls, there were significant associations between the SNP and HBV infection (A versus G: OR = 1.22, 95% CI = 1.08–1.39, *P* = 0.002; AG+AA versus GG: OR = 1.32, 95% CI = 1.12–1.56, *P* = 0.001). When comparing the Han Chinese (CHB) and spontaneously recovered people, there was also a significant association (A versus G: OR = 1.22, 95% CI = 1.08–1.37, *P* = 0.002). In conclusion, in the Caucasian population, the *RANTES* -403A allele is a risk factor of susceptibility to persistent HBV infection. The *RANTES* -403A/G polymorphism is likely to associate with the persistent infection of hepatitis B virus, regardless of virus clearance. More studies are needed to validate this relationship.

INTRODUCTION

Hepatitis B virus (HBV) is still a severe challenge to the global public health, leading to over 400 million infections all over the world [1]. Approximately, 5–10% of adult patients and 29–40% of child patients may not be able to clear HBV and will eventually progress into chronic hepatitis B (CHB) without elucidated mechanisms [2]. Many factors can lead to chronic HBV infection and further progress into cirrhosis and liver cancer, including host immune, viral replication level, genetics, HBV variants and others [3, 4].

RANTES (regulated on activation, normal T cell expressed and secreted) promotes the accumulation and activation of CD4+ T cells, CD8+ T cells, natural killer cells and dendritic cells (DCs), it is a powerful immune-regulatory chemokine in inflammatory disorders [5–7]. It acts as a ligand for CC receptor 5 (CCR5) that expressed on T cytotoxic cells, which were observed to be significantly decreased in CHB patients compared to healthy people [8]. Some studies have also suggested that the serum *RANTES* level in CHB patients was

significantly elevated, suggesting a correlation with the progress of disease, but the specific mechanisms were not clear [9, 10]. Recently, several polymorphisms of *RANTES* have been reported to associate with the risk of HBV infection, including -403A/G, -28C/G and In1.1T [11]. In Koreans, *RANTE*S polymorphism at position -403 did not show any effect on increased HBV infection risk [12]. However, a significant association was observed between *RANTE*S -403A/G and the risk of HBV infection in Saudi population [13] as well as in North Americans [14].

The relationship between *RANTES* -403A/G polymorphism and the risk of HBV infection are still controversial. The aim of this meta-analysis is to explore their relationship in a larger cohort.

RESULTS

A total of 35 relevant studies were selected for possible inclusion. Two of them were not performed in humans; seven studies were not focused on *RANTES*; four studies were vaccine related; eight were not case-control studies; one of them used the same dataset with a previous study; six studies did not analyze *RANTES* -403 polymorphism. According to our search strategy, eight case-control studies were eventually included in this meta-analysis [11–14, 17–20]. Specific selection process is displayed in the flow chart in Figure 1.

A total of 5502 individuals were curated in this meta-analysis of eight studies, including 2749 (49.96%) patients with persistent HBV infection and 2753 (50.04%) controls. Among the controls, 1256 were healthy individuals and 1497 were spontaneously recoveries (SRs) from HBV infection. All control individuals were in accordance with Hardy-Weinberg equilibrium. Two studies were of Caucasians [13, 14]; the others were focused on Asians [11, 12, 17–20]. However, two studies only presented the allelic data, our attempts of obtaining genotypic data from these two studies have failed. Therefore, we analyzed the allelic association between cases and controls from all the eight studies, and the genotypic association from six studies. The basic characteristics of eight studies are listed in Table 1.

The association between *RANTES* -403A/G alleles and the risk of persistent HBV infection was shown in Figure 2. There was strong heterogeneity (I^2 = 86.5%, p = 0.000 at -403A/G), therefore we applied the random-effects models. No significant association was found between *RANTES* -403A/G gene polymorphism and HBV infection in allelic model (OR = 1.04, 95% CI = 0.96–1.13, p = 0.34). The different genotypes : (a) AA versus GA: OR = 1.15, 95% CI = 0.93–1.42, p = 0.20; (b) AA versus GG: OR = 1.13, 95% CI = 0.91–1.41, p = 0.26; (c) GA versus GG: OR = 1.15, 95% CI = 1.00–1.32, p = 0.05; (d) GA+AA versus GG: OR = 1.17, 95% CI = 1.03–1.34, p = 0.02, were shown in Figure 3.The GG genotype was potentially related to the decreased risk of HBV infection.

Subgroup analyses based on ethnicity was also performed. In the Caucasian population, the A allele was significantly associated with a higher risk of HBV infection (OR = 1.68, 95% CI = 1.38–2.04, P < 0.001). Similarly, we also observed significant associations in different genotypic models (AG versus GG: OR = 1.85, 95% CI = 1.42–2.41, P < 0.001; AG+AA versus GG: OR = 1.75, 95% CI = 1.35–2.26, P < 0.001). However, in Asians, no significant association between the *RANTES* -403A/G allele polymorphism and HBV infection were observed (OR = 1.05; 95% CI = 0.96–1.16, p = 0.27) (Table 2).

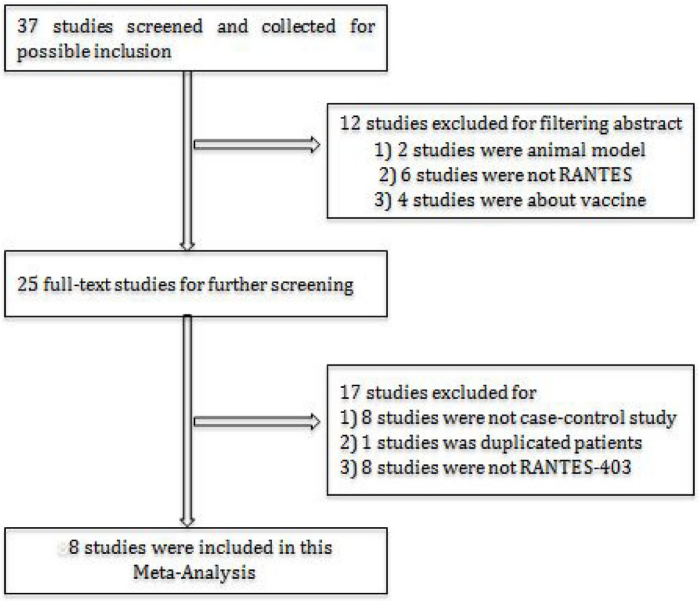


Figure 1: Flowchart of study selection in this meta-analysis.

Table 1: The basic characteristics of eight articles in this meta-analysis about the relationship between *RANTES*-403 polymorphism and chronic HBV infection

Author	Year	Ethnicity	Cases	Controls	Control type	Genotypes of cases				Genotypes of controls				Quality (stars)
						G/A	GG	AG	AA	G/A	GG	AG	AA	
Al-Qahtani	2012	Caucasian	484	473	Healthy	710/258	240	230	14	753/193	299	155	19	5
Chloe L. Thio	2008	Caucasian	181	316	SR	291/46	NR	NR	NR	514/190	NR	NR	NR	5
Heong JY	2007	Asian	607	350	SR	750/464	227	296	84	434/266	128	178	44	7
Sang Hoon Ahn	2006	Asian	349	106/243	Healthy/SR	414/284	128	158	63	415/283	36/85	55/118	15/40	6
DuanZP	2005	Asian	152	139	Healthy	198/106	64	70	18	162/98	52	58	20	5
Zhang C	2012	Asian	229	200/161	Healthy/SR	264/194	82	100	47	406/316	63/53	100/74	37/34	6
Byung Lae Park	2006	Asian	666	429	SR	755/535	NR	NR	NR	508/346	NR	NR	NR	6
Hsiu-Ting Tsai	2012	Asian	102	347	Healthy	126/78	42	42	18	538/156	205	128	14	6

SR: spontaneously recovered; NR: not reported. Quality: quality assessment according to the Newcastle-Ottawa Quality Assessment Scale.

We then stratified the controls into two types (healthy individuals [11–13, 18, 20] and SRs [12, 14, 17–19]). We found that *RANTES*-403A allele was a risk factor of persistent HBV infection when compared to healthy controls (A versus G: OR = 1.22, 95% CI = 1.08–1.39, $p = 0.002$; AG versus GG: OR = 1.29, 95% CI = 1.09–1.54, $P = 0.004$; AG+AA versus GG: OR = 1.32, 95% CI = 1.12–1.56, $P = 0.001$) (Table 3). Interestingly, when individuals with HBV infection were combined with SR and compared with controls [11–13, 18, 20], we and found there was also a significant difference between the new case group and healthy controls (A versus G: OR = 1.22, 95% CI = 1.08–1.37, $p = 0.002$).

Sensitivity analysis was performed by removing individual study at one time. This analysis showed there was no influence of each study on ORs. Publication bias was assessed by Egger's linear regression test and funnel plot for the included studies. Figure 4 revealed that there

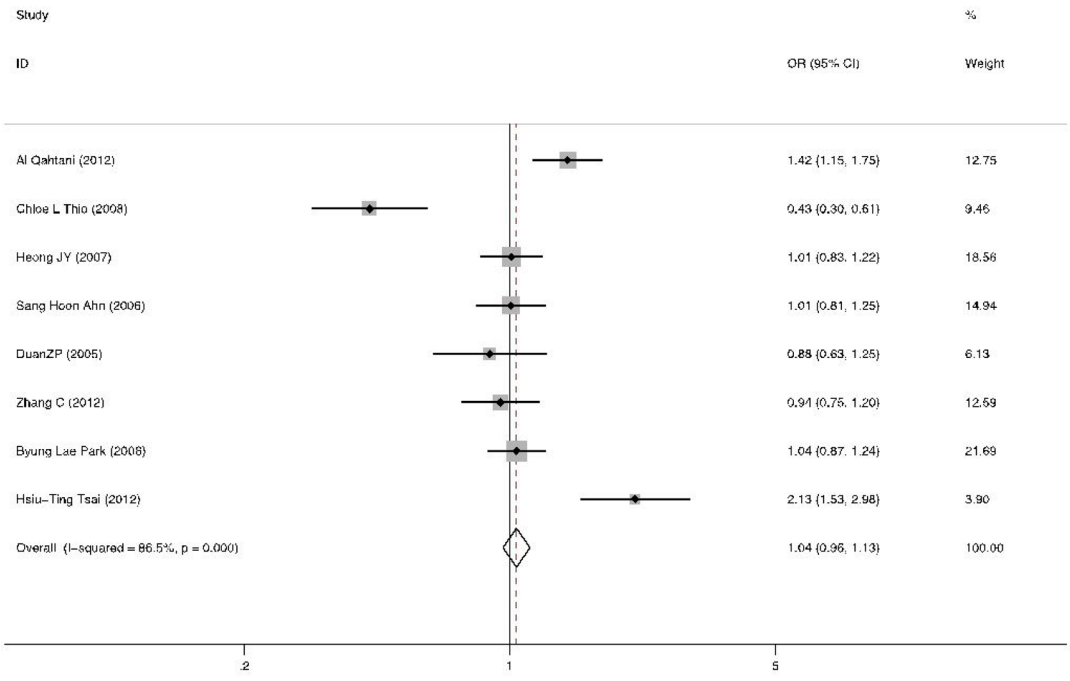


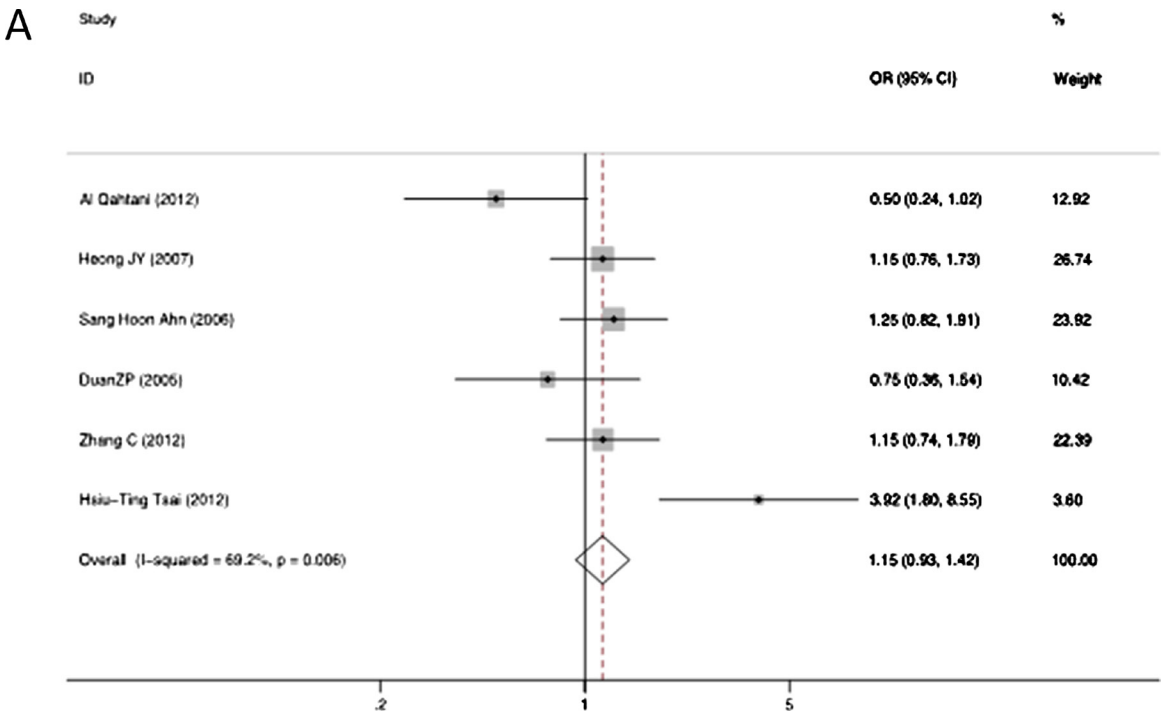
Figure 2: Forest plot of the risk of chronic HBV infection related to A allele versus G allele about *RANTES* -403A/G polymorphism in all studies. Black square means value of OR, and the size of the square means inversely proportional to its variance. Horizontal line means 95% confidence interval (CI) of OR. Black diamond means pooled results.

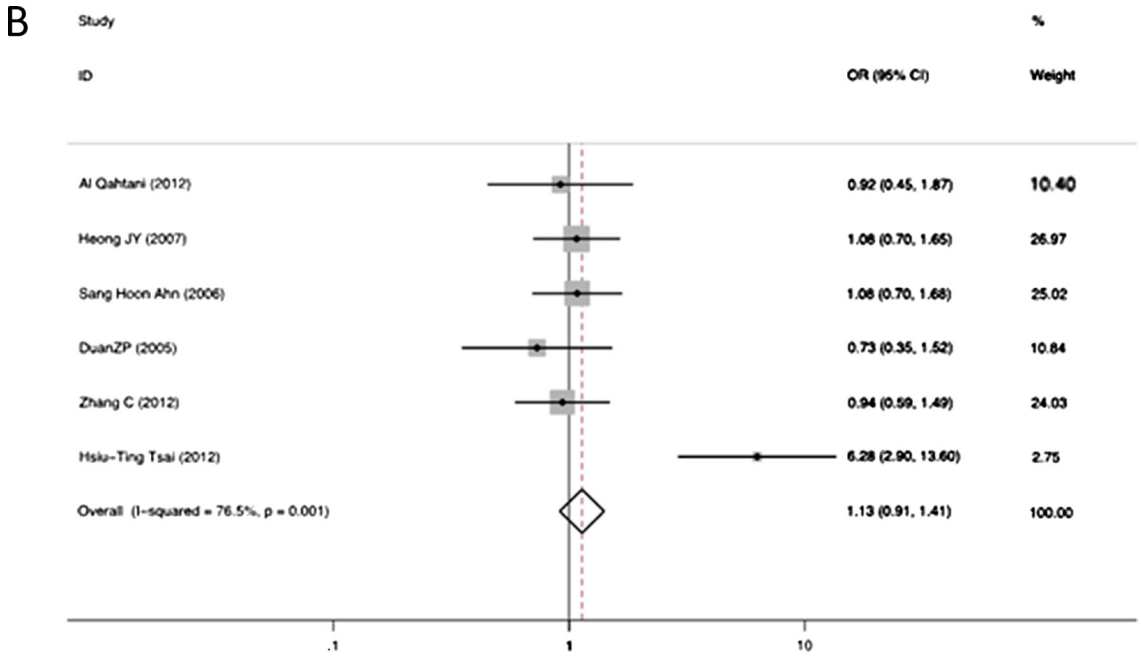
is no evidence of obvious asymmetry of the funnel plots, indicating no significant publication bias existed in this meta-analysis (Egger's test $p = 0.679$).

DISCUSSION

This is the first meta-analysis to investigate the relationship between the *RANTES* -403A/G polymorphism and risk for HBV infection. Eight studies were collected following stringent inclusion criteria in order to validate the association between *RANTES* -403A/G polymorphisms and persistent HBV infection. We demonstrated the importance of the *RANTES* -403A/G polymorphism in the HBV infection.

In the process of HBV infection, the immune system have a direct impact on the disease manifestation and outcome, which may induce hepatocellular damage [21]. The majority of adults with HBV infection may recover due to efficient immune response. The differences of immune mediators at the genetic level can influence the





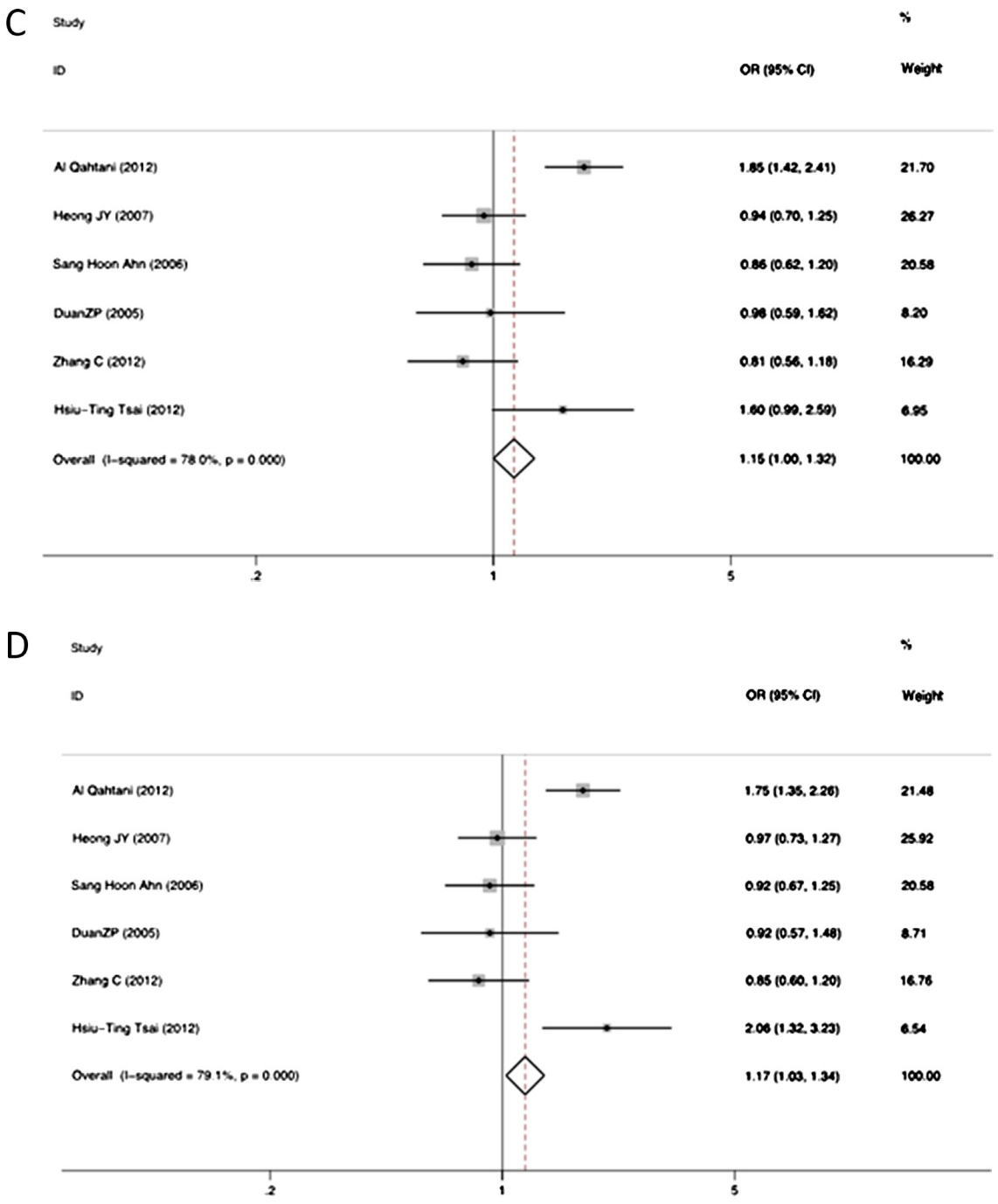


Figure 3: Forest plot of the risk of chronic hepatitis B infection progression related to RANTES gene -403 polymorphism of different genotypes: AA versus GA genotypes (**A**); AA versus GG genotypes (**B**); GA versus GG genotypes (**C**); GA+AA versus combined GG genotypes (**D**). Black square means value of OR, and the size of the square means inversely proportional to its variance. Horizontal line means 95% confidence interval (CI) of OR. Black diamond means pooled results.

host's immune ability to counter HBV infection [22–25]. Recently, chemokines and their receptors that were proved to play an important biological role in immune responses should arise more attention [26, 27].

Previous studies have suggested *RANTES* as one of the candidate genes in the development of persistent HBV infection. The *RANTES-CCR5* pathway have shed some light on viral clearance mechanisms, such as with hepatitis C virus [28, 29] and West Nile virus [30]. Studies have demonstrated that it plays an important role in sustaining CD8 T cell responses during the chronic infection [31, 32]. The mechanism of virus clearance is largely unknown and

Table 2: Subgroup analyses by ethnicity about association between *RANTES* gene -403 A/G polymorphism and susceptibility to chronic HBV infection

Genotype	Ethnicity	Cases	Controls	OR (95%CI)	*P*	Heterogeneity	
						df (*P*-value)	I^2(%)
A / G	Caucasian	304/1001	383/1267	**1.68 (1.38,2.04)**	**<0.001**	1 (0.96)	97
	Asian	1661/2507	1465/2463	1.05 (0.96,1.16)	0.27	5 (0.002)	74
AG/ GG	Caucasian	230/240	155/299	**1.85 (1.42,2.41)**	**<0.001**	0	
	Asian	666/543	711/622	0.96 (0.81,1.13)	0.59	4 (0.24)	28
AA / GG	Caucasian	14/240	19/299	0.92 (0.45,1.87)	0.81	0	
	Asian	230/543	204/622	1.16 (0.92,1.46)	0.21	4 (0.0003)	81
AG+AA/ GG	Caucasian	244/240	174/299	**1.75 (1.35,2.26)**	**<0.001**		
	Asian	896/543	915/622	1.01 (0.87,1.18)	0.87	4 (0.02)	65

Table 3: Subgroup analyses by controls types about association between *RANTES* gene -40 A/G polymorphism and susceptibility to chronic HBV infection

Genotype	Control types	Cases	Controls	OR (95%CI)	*P*	Heterogeneity	
						df (*P*-value)	I^2(%)
A/G	SR	1523/2474	1142/1924	0.93 (0.84,1.03)	0.15	4 (0.0003)	81
	HC	920/1712	706/1806	**1.22 (1.08,1.39)**	**0.002**	4 (0.0004)	80
	Overall	1965/3508	1848/3730	1.04 (0.96,1.13)	0.34	7 (<0.001)	87
AG/GG	SR	554/437	370/266	0.91 (0.74,1.11)	0.36	2 (0.96)	0
	HC	600/556	496/655	**1.29 (1.09,1.54)**	**0.004**	4 (0.001)	78
	Overall	896/783	866/921	1.15 (1.00,1.32)	0.05	5 (0.0004)	78
AA/GG	SR	194/437	118/266	1.02 (0.77,1.34)	0.89	2 (0.87)	0
	HC	160/556	105/655	1.24 (0.92,1.66)	0.16	4 (0.0004)	80
	Overall	244/783	223/921	1.13 (0.91,1.41)	0.26	5 (0.0007)	76
AG+AA/GG	SR	748/437	488/266	0.94 (0.77,1.13)	0.5	2 (0.94)	0
	HC	760/556	601/655	**1.32 (1.12,1.56)**	**0.001**	4 (0.0009)	79
	Overall	1089/921	1140/783	0.85 (0.75,0.97)	0.02	5 (0.0002)	79

SR: spontaneously recovered; HC: healthy; OR: odds ratio; CI: confidence interval; df: degrees of freedom.

needs to be solved. To date, there were a series of *RANTES* polymorphisms been reported, including -403A/G, -28C/G, intronic variant *INT*1.1T/C and 524T/C [11–14, 17–20]. They were involved in viral and non-viral diseases, such as AIDS, tuberculosis, type-1 diabetes, coronary artery disease, systemic lupus [33–37]. Different *RANTES* polymorphisms have different effects on the risk of HBV infection. The conclusions were inconsistent throughout different populations and studies [11–14, 17–20]. Relevant meta-analyses reported that the *RANTES* -28G allele may be beneficial to the resistance to HIV-1 infection among Asians [38, 39].

Eight studies were included in this meta-analysis based on standardized search strategy, which demonstrated that *RANTES* -403A/G polymorphism has significant association with the susceptibility to persistent HBV infection among Caucasians in allelic and genotypic models. Subgroup analysis by control types showed that *RANTES* -403A allele might be the risk factor of HBV infection when compared to healthy controls but not to the SR controls. When combined the cases and SRs and compared them with the healthy controls we found there was also a significant difference in allelic model.

Subgroup analysis by ethnicity revealed a significant association between the *RANTES* -403A/G polymorphism and HBV infection in the Caucasian population but not in the Asian population. The controversial results might come from the variations of ethnicity, sample size, and haplotypes. When stratified by different control groups, the allele was a risk factor compared to the healthy group,

instead of the SR control group. We inferred that *RANTES* -403A/G gene polymorphism may be associated to HBV infection, instead of virus clearance. It was demonstrated that *RANTES* -403A was associated with the susceptibility to HBV infection, but in the case of clearance progression, other factors need to be explored.

Although meta-analysis is a predominant statistical method, there are still some limitations. Firstly, there was a significant heterogeneity in our study. Secondly, only eight studies were collected and as few as six had specific genotypic data. Insufficient sample size may cause some deviation in data analysis. Therefore, additional studies are needed for further investigation. Thirdly, some unpublished negative results, have not been included. Lastly, we only analyzed the association between -403A/G and HBV infection without taking account of relevant environmental factors, such as alcohol consumption and smoking. Gene-environment interaction may be an important risk factor for the HBV infection, therefore to analyze the interaction may be essential. In the present study, we were unable to perform such analysis due to insufficient data regarding environmental factors in all included studies.

In conclusion, this meta-analysis demonstrated that there was no significant difference between *RANTES* -403A/G gene polymorphism and the outcome of persistent HBV infection. But according to the subgroup analyses, the A allele plays a risk role in HBV infected patients in the Caucasian population. Further studies are needed to verify the this association.

MATERIALS AND METHODS

Search strategy

Literature search was performed by two independent researchers in PubMed/MEDLINE (last updated on 1 January 2017), CNKI (last updated on 1 January 2017) using the following keywords: ('CCL5' or 'chemokine ligand 5' or '*RANTES*' or 'regulated upon activation normal T cell expressed and secreted') and ('HBV' or 'hepatitis B' or 'liver disease' or 'chronic hepatitis B virus') and ('polymorphism' or 'gene polymorphisms' or 'gene mutation' or 'gene variants'). No language restrictions were used in the search. Consensuses on controversial issues were reached through consultation between two researchers, or with our supervisor (Zheng Zeng).

Criteria of inclusion and exclusion

The inclusion criteria were as follows: (a) evaluating the relationship between *RANTES* -403A/G gene polymorphisms and HBV infection; (b) case-control studies; (c) containing abundant genotype data to calculate the odds ratios (ORs) with 95% confidence intervals (CIs); (d) full-text; (e) human studies; (f) using the following diagnostic criteria: patients with the serum hepatitis B surface antigen (HBsAg) positive for ≥6 months were diagnosed as persistent HBV infection; individuals with HBsAg(–), anti-HBc(–) and anti-HBs(–) were defined as

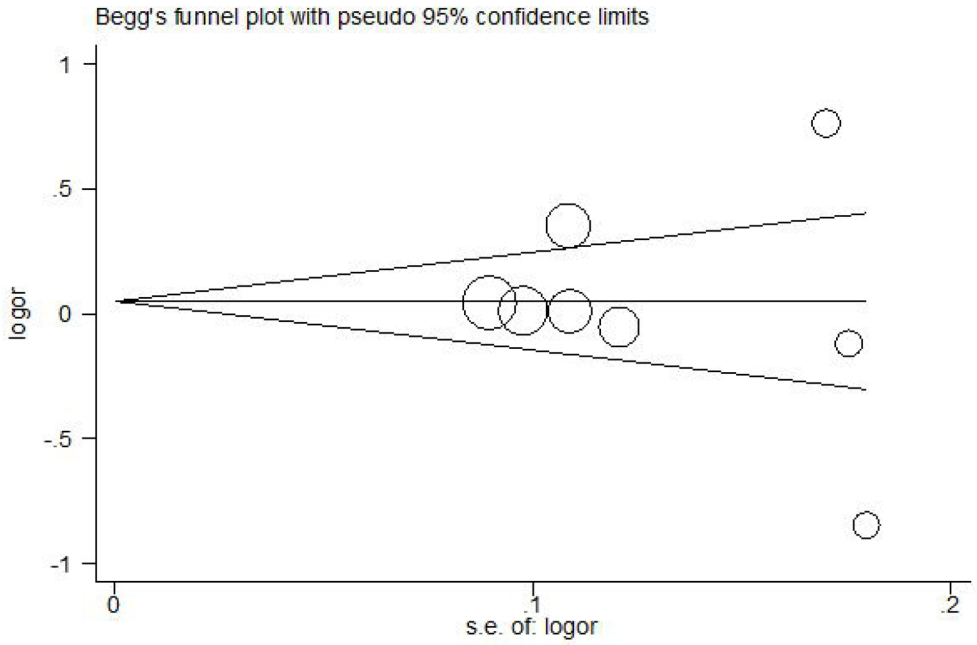


Figure 4: Funnel plot association between RANTES -403A/G polymorphism and chronic HBV infection. Log OR means nature logarithm of OR (odds ratio). Horizontal line means the summary estimate, while the sloping lines mean the expected 95% confidence interval. Egger's test $p = 0.679$.

health controls (HC); individuals with HBsAg(–), anti-HBc(+), and anti-HBs(+) were defined spontaneously recovered (SR) controls. The criteria of excluding studies were: (a) the data of the studies were overlapped; (b) no full-text; (c) not a case-control study; (d) not in line with the diagnostic criteria.

In the meantime, we applied Newcastle-Ottawa Quality Assessment Scale (NOS) to assess the quality of all the included case-control studies. Studies with low quality (<5 stars) were excluded.

Data extraction

The following characteristics were selected from each study: first author's name, year of publication, country and ethnicity of the study population, clinical subtype, numbers of the cases and controls, genotyping methods, sex of the cases and controls, mean age of the cases and controls and the HWE test results. The control groups included healthy individuals (HC) and spontaneous recovered individuals (SR). The case group included all clinical subtypes, such as asymptomatic patients, patients with chronic hepatitis B, liver cirrhosis (LC), or hepatocellular carcinoma (HCC).

Statistical analysis

The odds ratios (ORs) and the 95% confidence intervals (CIs) were calculated to assess the relationship between *RANTES* -403 gene polymorphism and chronic hepatitis B according to gene allele and genotype: the allelic model (A allele versus G allele), the homozygous model (AA versus GG), the heterozygous model (AA versus GA), the dominant model (GA+AA versus GG). Subgroup analyses were also performed based on clinical control group types and ethnicities. Heterogeneity was estimated by Cochrane's Q-test and I^2 measurement, which means the proportion of variability across studies is due to heterogeneity rather than by chance. $I^2 > 50\%$ indicated a significant heterogeneity [15] and the random-effects model would be applied. Otherwise, the fixed-effects model would be applied. The quality and reliability of this meta-analysis were evaluated by sensitivity analysis through excluding one study each time. The publication bias was assessed by the Egger's test and funnel plots [16]. All Quantitative analysis was performed using Stata 11.0 software (StataCorp LP, College Station, TX, USA).

Abbreviations

CCR5: CC receptor 5; CI: confidence interval; DC: dendritic cell; HC: healthy control; HCC: hepatocellular carcinoma; HBsAg: hepatitis B surface antigen; HBV: hepatitis B virus; HWE: Hardy-Weinberg equilibrium; LC: liver cirrhosis; OR: Odds ratio; SR: spontaneous recovered.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest relevant to this article to disclose.

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