A meta-analysis evaluating the relationship between IL-18 gene promoter polymorphisms and an individual's susceptibility to HCV infection

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Abstract

Background : **Several observational studies have investigated interleukin-18 (IL-18) gene polymorphisms with regard to susceptibility to hepatitis C virus (HCV) infection, but the results have been inconsistent.**

Aim : **To evaluate the relationships between functional polymorphisms in the IL-18 gene and an individual's susceptibility to HCV infection, a meta-analysis was performed. Methods: A literature search was conducted using the PubMed, EMBASE, Web of Science and China BioMedicine databases to investigate the correlation between IL-18 gene polymorphisms and susceptibility to HCV infection. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.**

Results : **The polymorphisms IL-18-607 C>A and -137 G>C were correlated with susceptibility to HCV infection in Asian populations. However, there was no evidence indicating a correlation between either of these polymorphisms and susceptibility to HCV infection in Caucasian populations.**

Conclusion : **Our current meta-analysis suggests that the -607 C>A and -137 G>C polymorphisms in the IL-18 gene promoter play important roles in determining the response to HCV in Asian populations. More studies with larger sample sizes are needed to evaluate the associations between IL-18 genetic polymorphisms and HCV infection risk.** (Acta Gastroenterol. belg., **2018**, 81, **39-44**).

Keywords : IL-18, HCV, polymorphisms, meta-analysis.

1. Introduction

Hepatitis C virus (HCV) is a leading cause of liver disease worldwide. An estimated 170 million chronic infections with HCV occur globally, with a 1-2% prevalence rate in most countries (1). HCV evades clearance mechanisms and establishes persistent infection in the majority of cases, leading to cirrhosis in 5-25% and hepatocellular carcinoma in 2% of infected people, whereas approxi-mately 80% of infected patients fail to clear the virus and develop a chronic infection (2,3). The relationships between HCV and the host defence system have yet been clearly defined. It is general believed that the outcome of acute HCV infection is determined by the competence of the host's innate and adaptive immune responses. HCV clearance is associated with vigorous HCV-specific CD4_and CD8_T cell responses (4,5). By contrast, the lack of a sustained HCV-specific T-cell response is associated with the development of persistent infection (6). Therefore, the host genetic factors that control immune responses may play important roles in determining the outcome of the HCV infection. Host genetic factors that have been implicated in HCV infection or persistence mainly include certain alleles in HLA classes I and II and cytokine genes. Cytokines likely play important roles in the immune regulation that controls HCV clearance or persistence and the resulting pathogenesis (7-11).

Human interleukin-18 (IL-18), a proinflammatory cytokine, induces interferon-gamma and tumour necrosis factor-alpha and enhances the cytotoxicity of NK cells and FasL expression (12). IL-18 polymorphisms in the promoter region have been associated with many kinds of diseases. In HCV infection, IL-18 is significant up-regulation in the inflammatory infiltrate, suggesting a role of this cytokine in the chronic cellular immune response towards hepatocytes during the course of the disease (13,14). We hypothesized that promoter polymorphisms known to modulate IL-18 expression influence the outcome of HCV infection. The IL-18 gene promoter -607 C>A (rs1946518) and -137 G>C (rs187238) polymorphisms are two of the most common single-nucleotide polymorphisms (SNPs). The -607 C to A mutation polymorphism alters a cyclic adenosine monophosphate responsive element protein-binding site, resulting in decreased IL-18 transcription. The -137 G to C polymorphism can changes the binding site of the histone 4 transcription factor-1 nuclear factor (15).

The association between polymorphisms in the IL-18 gene and susceptibility to HCV infection has been investigated in several studies. However, these studies have yielded different or even contradictory results. Therefore, we performed a meta-analysis to derive a more precise estimation of the association to help us better understand the relationship between the polymorphisms of the IL-18 gene and susceptibility to HCV infection.

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2. Materials and Methods

2.1 Literature search

PubMed, EMBASE, the Wangfang database, the Web of Science and China Biology Medicine (CBM) database, and China National Knowledge Infrastructure (CNKI) were searched starting before September, 2016. The following terms were used: Interleukin-18 (IL-18), polymorphism (or SNP) and Hepatitis C virus (HCH, or HCV). The search results were retrieved, and the references were checked to find other potential publications. Decisions about controversial studies were made through discussions between the authors in our group.

2.2 Inclusion and exclusion criteria

The following criteria were met in the studies included in this meta-analysis : (1) the case-control studies were focused on the associations between IL-18 polymorphisms and their effects on HCV infection or persistent infection ; (2) all patients diagnosed with HCV were confirmed by positive HCV laboratory results ; and (3) the data on the frequencies of the alleles or genotypes were sufficient. Articles were excluded when they were: (A) not case-control studies on the associations between IL-18 polymorphisms and HCV infection or persistent infection, (B) duplicates of publications, (C) publications without complete data, and (D) meta-analyses, letters, abstracts or reviews. If there were overlapping studies by the same author, the study with the largest sample size was included.

2.3 Data extraction

Two authors (Chen and M. Jing) independently read the full eligible studies and extracted the relevant data from the published studies into a standardized form. Disagreement was resolved by discussion between the three authors (Zhang, Yuan and S. Jing). A final decision was made through a majority of votes. For each study, the following data were collected: the first author's surname, year of publication, country, ethnicity and the total number of cases and controls genotyped. According to the differences in physical characteristics, the world races are roughly divided into three major ethnic groups, namely Mongolian race (yellow race), Caucasian race (white race), Negro race (black race). Because of the different genetic background, our study was classified according to ethnicity, chosen two different models categorized as Asian (yellow race) or Caucasian. The Hardy-Weinberg equilibrium (HWE) of the genotypes distribution was determined in the healthy control groups.

2.4 Statistical analysis

Fisher's exact test was used to assess whether the frequencies of the genotypes in the healthy controls were consistent with the HWE, and a p-value <0.05 disqualified the study. Odds ratios (ORs) with 95% confidence intervals (CIs) were measured for the IL-18 polymorphism and HCV infection. The statistical significance of the pooled ORs was determined using the additive genetic model, dominant model and recessive model separately. Heterogeneities were estimated by the Q test with a p-value <0.05 indicating statistically significant heterogeneity. If the p-value was less than 0.1, a random effects model was used to pool the results. Otherwise, a fixed effects model was used.

Publication biases were detected with the Begger's test (funnel plot method) and Egger's test (p<0.05 indicated statistical significance) (16). Sensitivity analysis was used to evaluate the consistency of the pooled results by omitting each study.

All statistical analyses were performed using STATA Version 12.0 software for Windows (Stata Corp, College Station, TX).

3. Results

3.1 Characteristics of the included studies

After eligible publications were carefully identified according to the flow chart in Fig.1, eleven studies (17-26) with 1826 cases and 2034 controls describing -607 C>A genotypes and 1962 cases and 2559 controls describing -137 G>C genotypes were included in the meta-analysis (Table 1). Each study presented the distributions of the genotypes in both the cases and controls from independent sampling. Two studies[23, 25] were not consistent with the HWE and were excluded from the meta-analysis.

3.2 Meta analysis

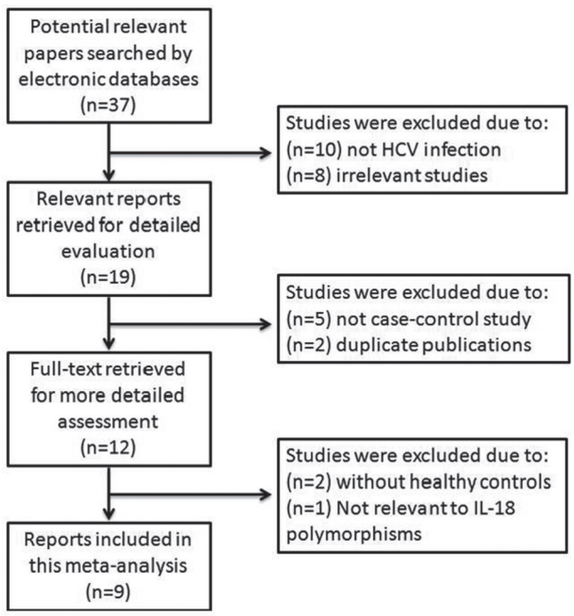

Fig. 1. — Flow diagram of the literature search and study selection process.

Table 1. — **The Characteristics of studies included the association of IL-18 polymorphisms with susceptibility to HCV infection**

Author	year	Case			Control			P*	population	pop1
		CC/GG	CA/GC	AA/CC	CC/GG	CA/GC	AA/CC			
IL-18 -607C>A polymorphism										
Mandour[17]	2014	40	63	20	39	58	26	0.56	Egyptians	Caucasian
Imran[18]	2014	55	60	25	32	53	35	0.19	Pakistani	Asian
Farid[19]	2013	46	22	12	5	4	6	0.07	Egyptians	Caucasian
Ji[20]	2013	52	108	39	39	96	45	0.36	Chinese	Asian
Cheikhrouh[21]	2011	30	44	26	26	50	24	0.99	Tunisian	Caucasian
Haas[22]	2009	276	347	134	300	369	122	0.63	German	Caucasian
Manohar[23]	2009	23	145	72	50	176	124	0.32	Indian	Asian
Bouzgarrou[24]	2008	24	38	19	21	44	17	0.49	Tunisian	Caucasian
Sivalingam[25]	2003	13	59	2	45	162	28	3.3E-09	Chinese	Asian
Sivalingam	2003	12	10	1	10	12	0	0.08	Indian	Asian
Sivalingam	2003	5	4	0	4	9	3	0.60	Malaysian	Asian
IL-18 -137G>C polymorphism										
Imran[18]	2014	57	70	13	43	61	16	0.44	Pakistani	Asian
Farid[19]	2013	34	32	14	6	5	4	0.21	Egyptians	Caucasian
Ji[20]	2013	158	38	3	122	53	5	0.79	Chinese	Asian
Liu[26]	2011	194	57	8	462	163	23	0.07	Chinese	Asian
Cheikhrouh[21]	2011	53	33	14	44	44	12	0.84	Tunisian	Caucasian
Haas[22]	2009	386	315	56	439	299	53	0.83	German	Caucasian
Manohar[23]	2009	126	52	62	218	59	73	1.3E-28	Indian	Asian
Bouzgarrou[24]	2008	38	31	12	35	35	12	0.51	Tunisian	Caucasian
Sivalingam[25]	2003	54	17	3	182	51	2	0.44	Chinese	Asian
Sivalingam	2003	18	5	0	17	5	0	0.55	Indian	Asian
Sivalingam	2003	6	3	0	7	7	2	0.90	Malaysian	Asian

The associations between the IL-18 gene promoter -607 C>A and -137 G>C polymorphisms and susceptibility to HCV infection are shown in Table 2 and Figs. 2-5. The results suggest that there were significant associations between both -607 C>A and -137 G>C and an individual's susceptibility to HCV infection in Asian populations (for -607 C>A : A/A vs. C/C : OR 0.892, 95% CI 0.709-0.971, $p = 0.020$; A/A vs. C-carriers : OR 0.710, 95%CI 0.551-0.915, $p = 0.008$. for -137 G> C : C/C vs. G/G : OR 0.821, 95% CI 0.685-0.985, $p = 0.034$; C-carriers vs. G/G : OR 0.791, 95% CI 0.637-0.981, $p = 0.033$). However, there was not a significant association between -607 C>A or -137 G>C and an individual's susceptibility to HCV infection in the Caucasian populations.

3.3 Publication bias evaluation

Begg's funnel plot and Egger's linear regression test were performed to assess publication bias in the included studies. The results of Egger's test ($p>0.05$), and Beggar's test ($p>0.05$) provided statistical evidence for the funnel plot symmetry (Table 2).

3.4 Sensitivity analysis

A sensitivity analysis was performed to assess the influence of each individual study on the pooled ORs by omitting individual studies. No individual study significantly affected the pooled ORs of the association

Table 2. — **ORs and 95%CI for IL-18 polymorphisms with susceptibility to HCV infection under different genetic models**

IL-18 polymorphisms	Genetic model	Population	Pooled OR[95% CI]*P*	Heterogeneity P-value	Begg's test P-value	Egger's test P-value
-607C>A	Additive(A vs. C)	Caucasian	1.012[0.898-1.141]0.843	0.086	0.327	0.074
		Asian	0.892[0.709-0.971]0.020	0.142	0.327	0.349
		Overall	0.941[0.855-1.035]0.211	0.027	0.166	0.004
	Dominant(A-carriers vs. C/C)	Caucasian	0.988[0.829-1.177]0.892	0.418	0.050	0.033
		Asian	0.852[0.648-1.120]0.251	0.049	0.624	0.548
		Overall	0.946[0.817-1.097]0.465	0.112	0.083	0.000
	Recessive(A/A vs. C-carriers)	Caucasian	1.060[0.854-1.316]0.599	0.128	0.142	0.150
		Asian	0.710[0.551-0.915]0.008	0.614	1.000	0.815
		Overall	0.895[0.759-1.054]0.184	0.087	0.386	0.169
-137G>C	Additive(C vs. G)	Caucasian	1.070[0.931-1.230]0.338	0.421	0.497	0.046
		Asian	0.821[0.685-0.985]0.034	0.181	0.573	0.857
		Overall	0.970[0.869-1.082]0.583	0.081	0.411	0.000
	Dominant(C-carriers vs. G/G)	Caucasian	1.093[0.916-1.305]0.324	0.249	1.000	0.188
		Asian	0.791[0.637-0.981]0.033	0.335	0.851	0.886
		Overall	0.958[0.836-1.098]0.540	0.092	0869	0.088
	Recessive(C/C vs. G-carriers)	Caucasian	1.071[0.780-1.470]0.673	0.806	0.042	0.334
		Asian	0.808[0.494-1.320]0.395	0.311	0.573	0.744
		Overall	0.984[0.755-1.283]0.907	0.585	0.622	0.395

between the -607 C>A or -137 G>C and an individual's response to HCV, indicating statistical stability.

4. Discussion

HCV infected patients have a markedly increased mortality rate, and there is no effective treatment, vaccine or post-prophylaxis. The outcome of infection is determined by the immune response. IL-18 is an important regulator of the Th1/Th2 driven immune response. In the IL-18 gene regions (located on chromosome 11q22.2-q22.3 and containing six exons and five introns), many single nucleotide polymorphisms (SNPs) have been studied, such as -137G>C and -607C>A in the IL-18 promoter regions and, 148G>C and 105A>C in the regulatory gene sequences. The SNP -137G>C and -607C>A in the promoter of the IL-18 gene may potentially have an effect on IFN-g and the transcription factors of the gene. These promoter polymorphisms have been observed as susceptible for various diseases, and the combination of transcriptional activity and genetic susceptibility to HCV has been a research focus of the scientific community (15).

However, previous studies of -607C>A and -137G>C have produced inconsistent results. For example, in a Tunisian population, -607 C>A and -137G>C can be used as a positive predictor of HCV infection (27), but there is no significant difference in the frequencies of the-137 allelic distribution between HCV infection patients versus healthy controls (19). The 137 G allele has been associated with genetic susceptibility to HCV in a Chinese population (20). In contrast, Liu (26) showed that alterations including -607C>A and -137G>C, in the IL-18 gene, did not lead to HCV infection. In summary, it is possible that IL-18 point polymorphisms confer susceptibility to HCV occur in only in certain ethnicities. Using proper and representative HCV-based and population-based control subjects is necessary to reduce biases in genetic studies. The present study analyzed 1826 cases and 2034 controls with the -607 allele genotypes and 1962 cases and 2559 controls with the -137 allele genotyped. Subgroup analysis by ethnicity, found that -607C>A and -137 G>C correlated with an individual's susceptibility to HCV infection in Asian populations. Of course, we also should be aware of that -137 G>C correlated with an individual's susceptibility to HCV infection in Asian, the p values are > 0.03(<0.05) which is very borderline for a significant association, maybe pointing to has a little protective role in HCV infection than -607C>A. However, we failed to find any evidence

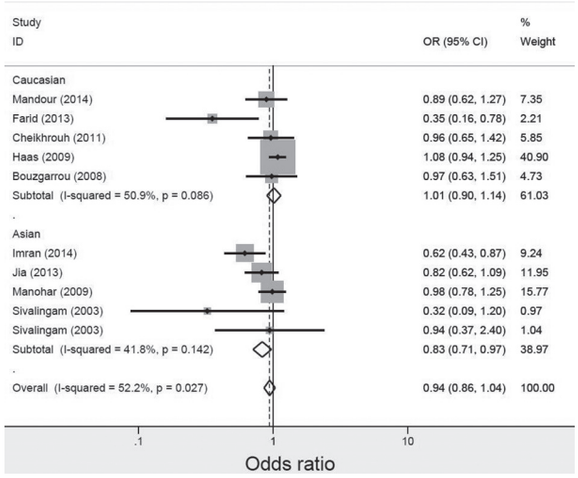

Fig. 2. — Forest plot of ORs of IL-18 -607C>A polymorphisms with susceptibility to HCV infection in Additive model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

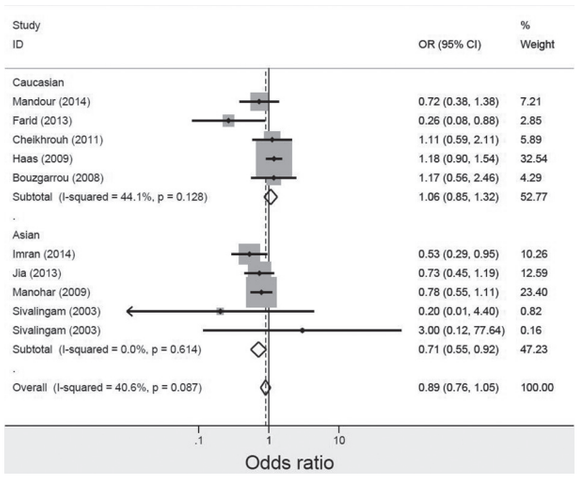

Fig. 3. — Forest plot of ORs of IL-18 -607C>A polymorphisms with susceptibility to HCV infection in Recessive model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

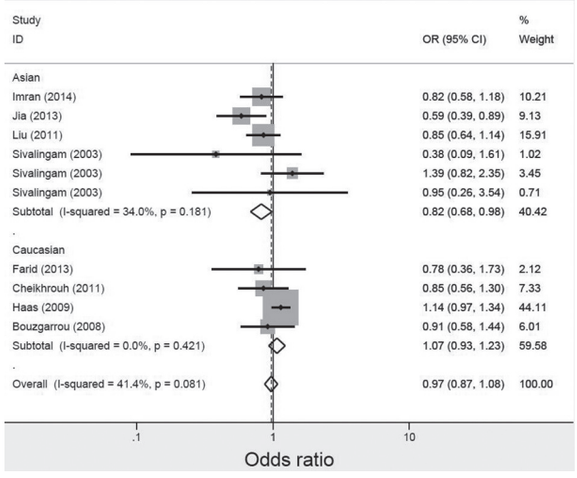

Fig. 4. — Forest plot of ORs of IL-18 -137G>C polymorphisms with susceptibility to HCV infection in Additive model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

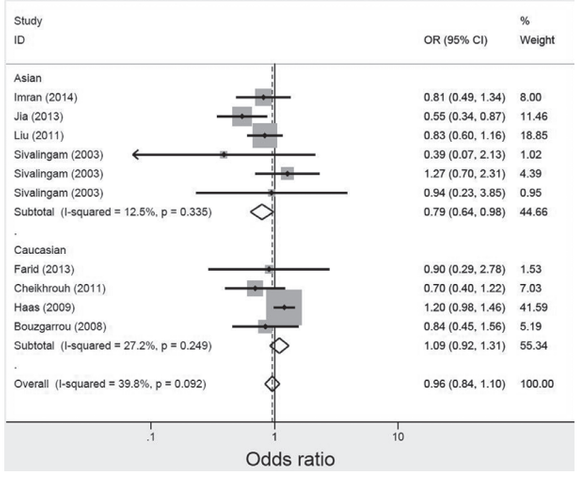

Fig. 5. — Forest plot of ORs of IL-18 -137G>C polymorphisms with susceptibility to HCV infection in Dominant model. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight. The diamond represents the pooled OR and 95% CI.

indicating a correlation between -607 C>A or -137 G>C and susceptibility to HCV infection in Caucasians. Ethnic or genetic factors cause this distinction between Caucasians and Asians. Furthermore, we need more evidence to support or deny the association between the IL-18 promoter polymorphisms and susceptibility to HCV infection in Caucasians.

To the best of our knowledge, this is the first meta-analysis to address the relationship between IL-18 polymorphisms and susceptibility to HCV infection in Asians and Caucasian. Similar to other meta-analyses, our study has some limitations. First, these small studies seemed to overestimate the true associations between the IL-18 genetic polymorphisms and an individual's response to HCV and susceptibility to HCV infection. Therefore, more studies with larger sample sizes are needed to provide a more representative statistical analysis ; in addition, studies in African populations are especially needed. Second, as a retrospective study, a meta-analysis may encounter recalls or selection bias, which can possibly influence the reliability of the study results[28]. Third, our lack of access to the original data

limited a further evaluation of potential interactions, such as gene-environment and gene-gene interactions, and a further haplotype analysis. Despite these limitations, we established an efficient literature search strategy based on computer-assisted, programmes as well as manual searches, which allowed us to include as many studies as possible. Nonetheless, explicit methods for study selection, data extraction, and data analysis were well designed before initiating. Finally, there was no evidence of publication bias in this meta-analysis and the sensitivity analysis indicated that our results were statistically robust.

5. Conclusion

Our meta-analysis suggests that the IL-18 -607C>A and -137 G>C genetic polymorphisms are associated with an individual's susceptibility to HCV infection in Asian populations, but there is no evidence exists that indicates a correlation between -607C>A or -137 G>C and HCV infection susceptibility in Caucasians. Further studies should evaluate the associations between IL-18 genetic polymorphisms and HCV infection risk.

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