Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Zheng MH. et al. (2013) Interleukin-28B rs12979860C/T and rs8099917T/G contribute to spontaneous clearance of hepatitis C virus in Caucasians. *Gene*, 518(2):479-482
Date of Review:	April 8, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** _____ **Level:** **Group** ☒ **Individual** ☐ **Other:** _____ **Target Population:** **patients infected with HCV or spontaneously cleared HCV** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** _____ **Country of Origin:** **China** **Language:** **English** ☒ **French** ☐ **Other:** _____

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	Meta-analysis; to estimate the effects of the two single nucleotide polymorphisms around interleukin-27B, rs12979860C/T and rs8099917T/G, with the spontaneous clearance of HCV infection.
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Information was not used for decision-making.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the results?	☐	☒	☐	Population of the results was confined in Caucasians, leading to insufficient epidemiological data of other ethnicities.

Are the best practices/methodology/results described applicable in developed countries?	☐	☐	☒	Similar analysis can be done, however the results of this study can only be extended to Caucasian populations.
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☐	☐	☒	
The research study/tool/data dictionary is easily accessed/available electronically	☐	☒	☐	Purchase required for downloading at http://www.sciencedirect.com/
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☒	☐	☐	The study was funded by the National Science and Technology Major Project of China, the Scientific Research Foundation of Wenzhou, Zhejiang Province, China, Health Bureau of Zhejiang Province, Research Foundation of Education Bureau of Zhejiang Province and Project of New Century 551 Talent Nurturing in Wenzhou
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Rs12979860CC and rs8099917TT had protective effects on HCV spontaneous clearance - Homozygous C allele at rs12979860 locus were nearly four times more likely to clear HCV spontaneously - Rs8099917 homozygote T allele had approximately three times increased rate of spontaneous

				HCV clearance
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☒	☐	Search of literature published up to January 11th, 2012
Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically: literature search conducted in Pubmed, EMASE and Cochrane Library
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Gene*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Existing data: 8 articles included

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Short Communication

Interleukin-28B rs12979860C/T and rs8099917T/G contribute to spontaneous clearance of hepatitis C virus in Caucasians☆

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ABSTRACT

Two single nucleotide polymorphisms rs12979860C/T and rs8099917T/G around interleukin-28B (IL28B) locus have been extensively investigated in their association with hepatitis C virus (HCV) spontaneous clearance. However, with the variable and even inconsistent results, it is necessary to conduct a meta-analysis. A literature search was conducted to seek articles about genetic variation of IL28B and spontaneous clearance of HCV. Odds ratio with 95% confidential interval were calculated to estimate their relationship. Furthermore, meta-regression analysis was performed to search for potential affective factors. A total of 8 studies including 2460 patients with chronic HCV infection and 1052 individuals with spontaneous HCV clearance met inclusion criteria, in which seven studies describing rs12979860 and three studies describing rs8099917. Analysis performed in Caucasian populations indicated that rs12979860CC and rs8099917TT contributed to HCV spontaneous clearance in both dominant model (CC vs. CT + TT, $P<1\times10^{-4}$; TT vs. TG + GG, $P<10^{-4}$, respectively) and co-dominant model (CC vs. CT, $P<1\times10^{-4}$, CC vs. TT, $P<1\times10^{-4}$; TT vs. TG, $P<10^{-4}$, TT vs. GG, $P=0.012$, respectively). Meta-regression analysis suggested that male proportion ($P=1\times10^{-5}$) and mean age ($P=1\times10^{-3}$) might weaken the effect of rs12979860CC, but HCV genotype 1/4 ($P=4\times10^{-4}$) might contribute to it. IL28B rs12979860CC and rs8099917TT genotypes contribute to spontaneous HCV clearance in Caucasians.

1. Introduction

Chronic hepatitis C has become a world health threat. There are 120 to 180 million people chronically infected with hepatitis C virus (HCV) in the world (Shepard et al., 2005). Approximately 30% of HCV infected patients can clear the virus spontaneously after acute infection and avoid the progression to chronic hepatitis C, which can develop into cirrhosis and hepatocellular carcinoma (Seeff, 1997).

Host genetics was assumed to influence the outcomes of HCV infection, in both the abilities to achieve sustained viral response (SVR) and spontaneous clearance. SVR was more frequently observed in patients of European ancestry than those of African ancestry (Conjeevaram et al., 2006). This ethnic difference was also found in spontaneous clearance of HCV (Thomas et al., 2000), even across individuals contaminated with the same strain of HCV (Kenny-Walsh, 1999).

Accumulating studies have assured that two single nucleotide polymorphisms (SNPs) around interleukin-28B (IL28B) locus, rs12979860C/T and rs8099917T/G, have the strongest association with the spontaneous clearance of HCV infection. These two SNPs had also been proved to associate with high SVR rate in chornic hepatitis C genotypes 1 and 4 (Shi et al., 2012). Recently, rs12979860CC (Thomas et al., 2009) and rs8099917TT (Rauch et al., 2010) genotypes were demonstrated to have protective effects on HCV infection in natural settings. However, the effects always came with variable magnitude and strength. In Caucasian, odds ratios (ORs) of rs12979860 ranged from 2.664 (Thomas et al.,

Abbreviations: CHC, chronic hepatitis C; CI, confidence interval; GWAS, genome-wide association study; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IFN, interferon; IL28B, interleukin-28B; kbs, kilobases; NA, not available; ORs, odds ratios; SNP, single nucleotide polymorphism; SVR, sustained viral response.

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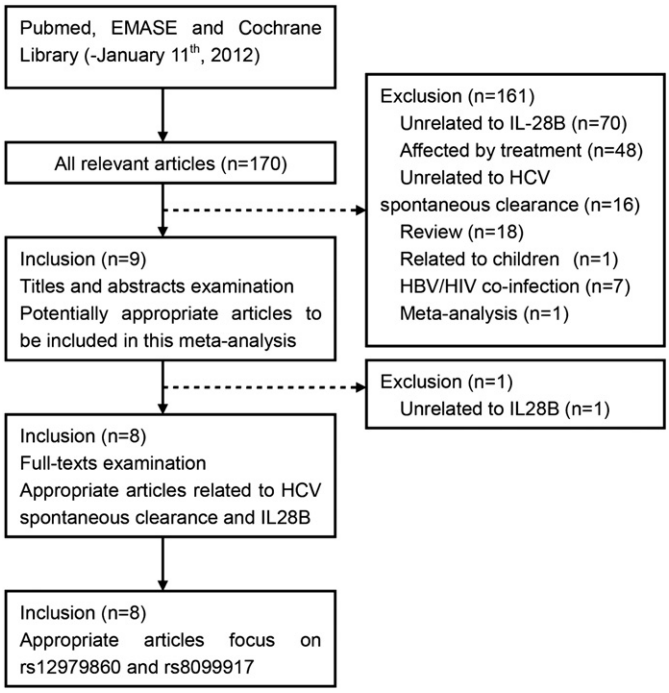

Fig. 1. Identification of appropriate articles to be included in this meta-analysis.

2009) to 7.391 (Tillmann et al., 2010), and that of rs8099917 from 2.467 (Rauch et al., 2010) to 4.531 (Grebely et al., 2010). Moreover, it was revealed that HCV spontaneous clearance was not associated with rs12979860 (Grebely et al., 2010) and rs8099917 (di Iulio et al., 2011). As a result, this meta-analysis was performed to derive a more precise estimation of the effects. Besides, meta-regression analysis was conducted to find potential affective factors.

2. Methods

2.1. Search strategy

A literature search updated to 11th, January 2012 was conducted in Pubmed, EMASE and Cochrane Library using the keywords related to IL28B in combination with HCV infection, with language restricted to English. Based on computer-based searches, scanning of the bibliographies of relevant articles and examination of review articles in this field, eligible genome-wide association studies and candidate gene studies concerning about the association between IL28B variants and outcomes of HCV infection in natural settings was carefully sought. Only published articles with full-text were included. The study was performed according to PRISMA statement.

2.2. Inclusion criteria and exclusion criteria

The inclusion criteria were set as follows: a) evaluation of the relationship between SNPs around IL28B locus and HCV spontaneous clearance in adult individuals; b) with HCV mono-infection population; c) unaffected by antiviral treatment. If the same population existed in more than one studies, the most recent and complete one was included. The exclusion criteria were set as follows: a) unrelated to IL28B; b) affected by treatment; c) unrelated to HCV spontaneous clearance; d) review articles; e) studies focus on children; f) HBV/HIV co-infection; and g) meta-analysis.

2.3. Definitions

Spontaneous clearance of HCV is defined as HCV seropositivity and undetectable HCV RNA without previous antiviral treatment. Chronic HCV infection is a necroinflammatory liver disease caused by persistent infection of HCV, which is defined as anti-HCV seropositivity and detectable HCV RNA by quantitative or qualitative assays (Rauch et al., 2010).

2.4. Data extraction

The main characteristics of each eligible study and the detailed data of frequency distribution of IL28B SNPs were carefully extracted according to a fixed protocol: study type, ethnicities, rsID around IL28B, number of patients with spontaneous clearance or chronic HCV infection, male proportion, mean age, HCV genotype and respective genotype frequency distribution of rs12979860 and rs8099917. This process was performed independently by two authors Shi KQ and Xiao DD. Disputes were resolved by discussion and consultation of another author Zheng MH, in which the final decision was made by a majority vote.

The data from included articles were not all fully presented. Some studies combined the patients co-infected with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) with the patients of HCV mono-infection. Frequency distribution of rs12979860T allele carriers or rs8099917G allele carriers was sometimes presented collectively. Furthermore, main characteristics of each population such as male proportion, mean age, and HCV genotype were not always available. So we designed questionnaires and contacted authors of each study by E-mail, fax or telephone numbers to ask for detailed data needed in this meta-analysis.

2.5. Statistical analysis

The pooled ORs with 95% confidential interval (CI) were calculated to address the effect of IL28B SNPs on the spontaneous clearance of HCV infection according to dominant model and co-dominant model.

Table 1
Main characteristics of all eligible studies included in this meta-analysis.

First author (year)	Ethnicity	rsID, allele	Study type	Patients		Male (%)	Mean age (year)	HCV genotype 1/4 (%)
				SC	CHC			
Thomas (2009)	Caucasian/others	rs12979860 C/T	Candidate gene study	147/241	299/321	79.6%	32.7	NA
Knapp (2011)	Caucasian/others	rs12979860 C/T	Candidate gene study	87/2	217/17	61.0%	42.5	NA
Dring (2011)	Caucasian	rs12979860 C/T	Candidate gene study	247	296	0.0%	27.4	100%
di Iulio (2011)	Caucasian	rs8099917 T/G rs12979860 C/T	GWAS Candidate gene study	27	44	0.0%	28.4	100%
Tillmann (2010)	Caucasian	rs12979860 C/T	Candidate gene study	67	123	0.0%	24.6	100%
Rauch (2010)	Caucasian	rs8099917 T/G	GWAS	135	779	60.2%	44.5	NA
Montes-Cano (2010)	Caucasian	rs12979860 C/T	Candidate gene study	69	284	41.1%	NA	80.6%
Grebely (2010)	Caucasian/others	rs8099917 T/G rs12979860 C/T	Candidate gene study	18/12	61/19	69.0%	33.5	40.9%

GWAS, genome-wide association study; SC, spontaneous clearance; CHC, chronic hepatitis C; NA, not available.

The significance of the pooled ORs was determined by Z-test, and was considered as statistically significant if a *P*-value <0.05.

Evaluated by Chi-square test, heterogeneity was considered significant if a *P*-value <0.1 (Higgins et al., 2003), in which case random-effects model (DerSimonian and Laird method) was used. Conversely, a fixed-effects model (Mantel–Haenszel method) was used when heterogeneity was insignificant. Begg's funnel plot and Egger's test were performed to examine potential publication bias. Obvious asymmetry of funnel plot meant evident publication bias (Stuck et al., 1998). The significance of the intercept was determined by the t-test suggested by Egger (*P*<0.05 was considered statistically significant) (Egger et al., 1997). Furthermore, meta-regression analysis was performed to search for potential factors which might affect the effects of IL28B SNPs on HCV spontaneous clearance, including male proportion, mean age and HCV genotype.

All calculations were performed using the Comprehensive Meta-Analysis computer program version 2 (Biostat, Englewood, NJ, USA).

3. Results

3.1. Baseline characteristics

A total of 8 studies with 2460 patients of chronic hepatitis C and 1052 individuals of HCV spontaneous clearance were sought through the process in Fig. 1, with seven studies describing rs12979860 and three studies describing rs8099917, the sample size ranging from 71 to 1008 (Table 1). We only calculated the pooled ORs with 95% CI in Caucasian population, for epidemiological genetic data concerning about other ethnic groups were so insufficient to carry out a meta-analysis.

3.2. Meta-analysis results

It is suggested that rs12979860CC contributed to spontaneous clearance of HCV. Dominant model (CC vs. CT + TT) indicated that rs12979860CC reduced the risk of chronic HCV infection (OR: 3.750, 95% CI: 2.421–5.808, $P<1\times10^{-4}$). Consistently, it was also protective in co-dominant model (CC vs. CT OR: 3.643, 95% CI: 2.417–5.489, $P<1\times10^{-4}$; CC vs. TT OR: 4.281, 95%CI: 2.046–8.956, $P<1\times10^{-4}$). Meanwhile, the similar effect was observed in rs809991TT in both dominant model (TT vs. TG + GG OR: 2.665, 95% CI: 1.819–3.904, $P<10^{-4}$) and co-dominant model (TT vs. TG OR: 4.601, 95%CI: 1.396–15.168, $P<10^{-4}$; TT vs. GG OR: 4.601, 95% CI: 1.396–15.168, $P=0.012$).

3.3. Meta-regression analysis results

Meta-regression analysis suggested that male proportion (slope: −0.014, 95% CI: −0.020 to −0.007, $P=1\times10^{-5}$) (Fig. 2A) and mean age (slope: −0.064, 95%CI: −0.103 to −0.026, $P=1\times10^{-3}$) (Fig. 2B) might weaken the effect of rs12979860CC on spontaneous clearance of HCV infection, whereas HCV genotype 1/4 (slope: 0.031, 95%CI: 0.014–0.048, $P=4\times10^{-4}$) (Fig. 2C) might strengthen this effect. For inadequate studies describing rs8099917, meta-regression was not conducted.

Heterogeneity was observed in both dominant and co-dominant model of rs12979860, but was not seen in that of rs8099917 (Table 2). Both Begg's funnel plot and Egger's test revealed that the publication bias was not evident.

4. Discussion

In this meta-analysis, we demonstrated that rs12979860CC and rs8099917TT had protective effects on HCV spontaneous clearance. Patients who were homozygous for the C allele at rs12979860 locus were nearly four times more likely to clear HCV spontaneously. This effect was negatively correlated with male proportion and age, and had a positive correlation with HCV genotype 1/4. At rs8099917 locus, T allele homozygote had a nearly three times increased rate of spontaneous HCV clearance.

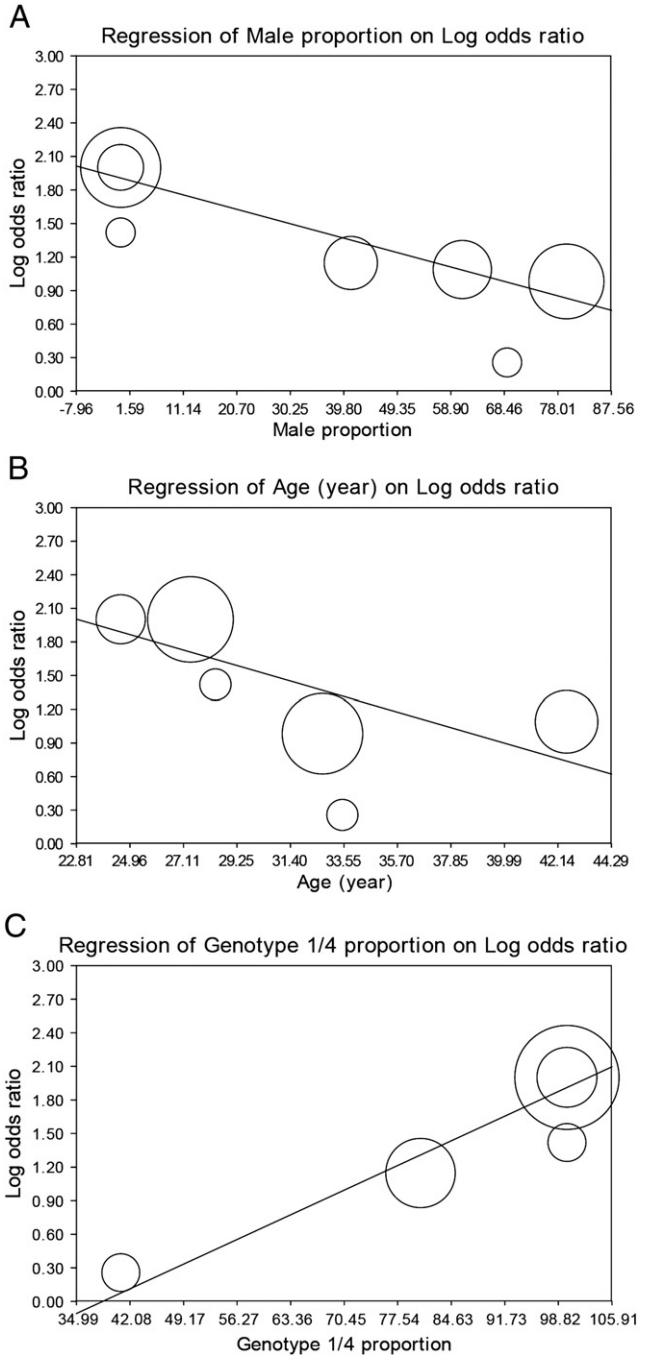

Fig. 2. Main results of meta-regression analysis. (A) Meta-regression analysis between male proportion among the studies and the effect of the rs12979860 on HCV spontaneous clearance in Caucasians. (B) Meta-regression analysis between mean age among the studies and the effect of the rs12979860 on HCV spontaneous clearance in Caucasians. (C) Meta-regression analysis between HCV genotype 1/4 among the studies and the effect of the rs12979860 on HCV spontaneous clearance in Caucasians. Log odds ratio which is the effect estimate for HCV spontaneous clearance in meta-analysis is shown in Y-axis. Characteristic of studies (male proportion, mean age, or HCV genotype) is shown in X-axis. Each circle represents a study with a size proportional to the sample size.

The results of this meta-analysis could help to generate a more comprehensive understanding of the impact of IL28B variants on HCV viral control. The mechanism explaining the association of IL28B gene and spontaneous HCV clearance remains unclear. But interferon-λ (IFN-λ) had been proved to be involved in the immune response to several

Table 2
Main results of pooled ORs in Caucasian population.

SNPs	Genetic models		ORs (95%CI)	*P*	*P* (Q-test)
rs12979860	Co-dominant model	CC vs. CT	3.643 (2.417,5.489)	0.000	0.006
		CC vs. TT	4.281 (2.046,8.956)	0.000	0.019
	Dominant model	CC vs. CT + TT	3.750 (2.421,5.808)	0.000	0.001
rs8099917	Co-dominant model	TT vs. TG	2.470 (1.671,3.650)	0.000	0.743
		TT vs. GG	4.601 (1.396,15.168)	0.012	0.995
	Dominant model	TT vs. TG + GG	2.665 (1.819,3.904)	0.000	0.655

SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.
P (Q-test): *P* value of Q-test for heterogeneity test. A random-effects model was used when *P* value for heterogeneity test <0.1; otherwise, a fixed-effects model was used.

pathogens in vivo and in vitro models, such as herpes simplex virus (Melchjorsen et al., 2006), cytomegalovirus (Brand et al., 2005), HIV (Hou et al., 2009) and HBV (Hong et al., 2007). Similarly, IL28B was found to inhibited HCV replication in dose- and time-dependent manner (Zhang et al., 2011). Rs12979860, located on chromosome 19q13 and 3 kilobases (kbs) upstream of the IL28 gene, and proximate rs8099917, located in an approximately 80-kb region which is 7554 base-pairs upstream the start codon of IL28B, encode endogenous antiviral cytokine interferon-λ3 (IFN-λ3). It was suggested that IFN-λ3 involved in host innate immune response to HCV infection in the early stage played a central role in the inhibition of HCV. IFN-λ3 binds to a cell-surface distinct class II cytokine receptor complex and activates the expression of interferon stimulating genes through JAK–STAT pathway (Kotenko et al., 2003; Marcello et al., 2006). In addition, it was believed that rs8099917G allele may interfere with transcription factors and influence gene expression of IFN-λ (Suppiah et al., 2009), which partially explains the observed increased risk of chronic HCV infection linked to this allele. It is appropriate to believe that rs12979860T allele interacts with the expression of IFN-λ3 in a similar way.

Meta-regression analyses examined three potential affective factors: male proportion, mean age and HCV genotype. The results were consistent with the previous three prospective studies in that female was a protective factor for HCV viral control (Micallef et al., 2006; Wang et al., 2007; Page et al., 2009). Young age (<40 years) was reported to be one of the indicators of HCV viral control (Munir et al., 2010). One explanation supporting the result that HCV genotype 1/4 might contribute to the protective effect of rs12979860CC was that HCV genotype 1/4 infected patients were less sensitive to viral control (Di Martino et al., 2011).

In diagnosis and treatment decision-making, unfavorable IL28B genotypes were highly associated with failure to clear HCV spontaneously and were strongly recommended for early therapeutic intervention. On the contrary, it might be more beneficial for those patients with rs12979860CC or rs8099917TT to have postponed treatment, taken the side effects of IFN-α into consideration.

There were some limitations of this meta-analysis that we should be concerned about. Firstly, the population of the results was confined in Caucasians, for insufficient epidemiological data of other ethnicities. Secondly, this meta-analysis was unable to eliminate the potential influence of linkage disequilibrium between rs12979860 and rs8099917 (Ge et al., 2009), and investigate other SNPs around IL28B locus. Finally, this mate-analysis, based on unadjusted estimates, could be more precise by the adjustment of other covariates including HCV viral load in early phase, family history, lifestyle and environmental factors.

In summary, this meta-analysis demonstrated that rs12979860CC and rs8099917TT contributed to the spontaneous clearance of HCV infection in Caucasians.

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