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Research Paper

Host genetic variations are associated with virological response to interferon therapy of chronic HCV in Han Chinese patients

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Abstract

Previous studies have suggested that host genetic polymorphisms may affect virological response to pegylated-interferon and ribavirin (PEG-IFN/ ribavirin) therapy in chronic HCV infection. *IL28B* and *MxA* are the most intensively studied genes in Chinese Han population. The current research is to summarize published data and evaluate the overall association of meaningful SNPs in these two genes with virological response to interferon-based therapy. Literature search was performed in online database and a systematic review was conducted based on the search results. Meaningful single nucleotide polymorphisms (SNPs) were summarized and analyzed for odds ratio (OR) and 95% confidence intervals (95% CI). Data manipulation and statistical analyses were performed by using STATA 12.0 and Review Manager version 5.1. Eighteen papers were included for final data analysis. Three SNPs of *IL28B* and two SNPs of *MxA* were found to be associated with higher sustained virological response (SVR) to interferon therapy. The ORs and 95% CIs of each variant were: *IL28B* rs8099917 TT (OR: 4.35, 95% CI: 3.10~6.12), *IL28B* rs12979860 CC (OR: 5.37, 95% CI: 3.95~7.31), *IL28B* rs7248668 CC (OR: 3.50, 95% CI: 2.30~5.35), *MxA* rs2071430 GT (OR: 2.03, 95% CI: 1.31~3.13), and *MxA* rs17000900 AC/AA (OR: 1.82, 95% CI: 1.17~2.83). The genotypes of *IL28B* rs8099917, rs12979860, rs7248668, *MxA* rs2071430, and *MxA* rs17000900 were strong SVR predictors for PEG-IFN/ ribavirin -treated HCV patients in Han Chinese population. Our findings suggest that host genetic variations are associated with virological response to interferon therapy of chronic HCV in Han Chinese patients.

Keywords: hepatitis C virus, therapy, virological response, *IL28B*, *MxA*, meta-analysis

INTRODUCTION

Hepatitis C virus (HCV) infection is a global health problem and results in chronic liver inflammation, cirrhosis or hepatocellular carcinoma. The global prevalence of persons with anti-HCV antibody has increased from 2.3% to 2.8% during 1990 to 2005, and east Asia is estimated to be a high prevalence area (> 3.5%)[1]. The estimated HCV prevalence of China is 2.2% with 30 million people infected by 2010[2].

The sign of successful therapy is a sustained virological response (SVR), in which HCV RNA remains

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undetectable at week 24 after treatment completion[3]. The currently recommended treatment to achieve better SVR is pegylated-interferon and ribavirin (PEG-IFN/ ribavirin) therapy for 24 or 48 weeks. Both host and viral factors accounted for patients′ different responses to therapy, including baseline viral load, liver fibrosis, HCV genotypes, mutations of the interferon sensitivity determining region, Th1/Th2 ratio, and body weight[4,5]. Side effects of treatment such as anemia and psychiatric adverse events (e.g. depression, anger-hostility and anxiety) lead to dose reduction and premature termination of HCV treatment[6,7].

During the acute infection stage of HCV, the host innate immune response is activated and IFN-α is induced to clear the virus. Numerous IFN-stimulated genes (ISGs) are involved in the clearance of viruses. Based on the current publications, interleukin 28B (*IL28B*) and myxovirus resistance A (*MxA*) are the two most intensively studied genes. IL28B can be induced by HCV or IFN-α. Chronic hepatitis C patients with favorable *IL28B* genotypes had lower level of ISGs and treatment with exogenous INF-α could increase the expression of ISGs to generate sustained viral response[8]. MxA is an IFN-induced protein and identified as the strongest specific antiviral protein. It inhibits HCV replication and protein synthesis by combining with virus nucleoprotein and therefore affecting early transcription of HCV RNA within the cytoplasm[9].

In 2009, three GWAS (genome-wide association study) studies reported that single nucleotide polymorphisms (SNPs) near the *IL28B* gene region may be associated with SVR of PEG-IFN/ribavirin treatment in HCV-infected patients from Japanese, Australians, European Americans, African Americans and Hispanics[10–12]. Thereafter, a number of studies were published on the association between host SNPs and treatment response in chronic HCV patients with different ethnicities and HCV genotypes[13–16]. Some researchers also investigated the correlation in Chinese Han population. However, the results are not consistent among different studies. Therefore, we performed a meta-analysis to summarize the impact of *IL28B* and *MxA* on PEG-IFN/RBV treatment in Han Chinese population.

MATERIALS AND METHODS

Literature search

Several online databases including PubMed, China National Knowledge Infrastructure (CNKI), and WanFang were used for literature search. Relevant articles published up to May 31, 2013 were searched using the following terms: 'HCV', 'hepatitis C virus', or 'chronic Hepatitis C'; 'SNP', 'polymorphism', or 'gene'; 'SVR', or 'sustained virological response'; 'IL-28B', 'rs8099917', or 'rs12979860'; 'MxA', 'MxA-88', or 'MxA-123'. To identify other potential relevant publications, the reference lists of all retrieved articles were manually searched. In addition, cited review articles were retrieved and perused for mention of any additional relevant articles. Only published studies with full text articles were included in the meta-analysis.

Data extraction

Two independent investigators assessed the selected papers for eligibility following the predefined procedure as shown in ***Fig. 1***. Exclusion criteria were: studies dealing with non-Han Chinese population; using other therapeutic schedules instead of PEG-IFN/ribavirin; patients with HBV or HIV coinfections; duplicate or overlapping reports; non-research articles; studies with insufficient data. Discrepancy about including an article or not was resolved by discussion, and another author was consulted if necessary. The following information, though some studies did not contain all of them, was then extracted from each included study: the first author, date of publication, journal of the publication, sample size, demographic data of the subjects, HCV genotype, duration of therapy, location of involved SNPs, and the distribution data of each allele.

Statistical analyses

Statistical analyses were performed using the Review Manager for Windows (version 5.1, the Cochrane Collaboration, Oxford, UK) and STATA software programs (version 12.0, STATA Corporation, College

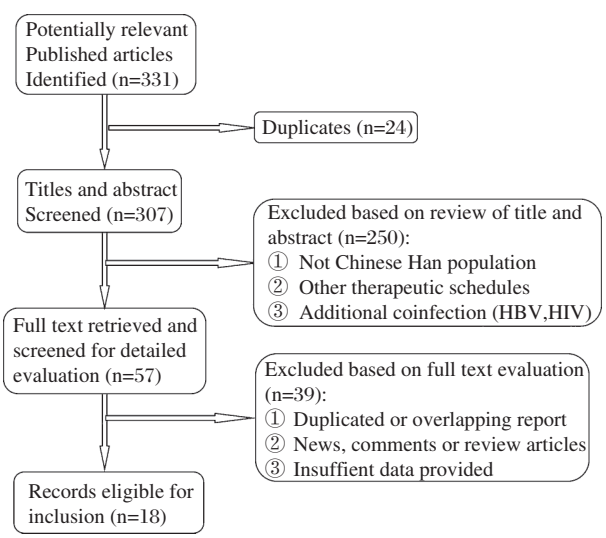

***Fig. 1* Study selection flow diagram.** HBV, hepatitis B virus; HIV, human immunodeficiency virus.

Station, TX, USA). The association strength between *IL28B* and *MxA* SNPs and SVR in HCV patients treated with PEG-IFN/RBV was determined by calculating the respective odds ratio (OR) and 95% confidence intervals (CI). The significance of the pooled OR was determined by *Z*-test, and *P*-value of less than 0.05 was considered significant. Two meta-analysis models for dichotomous outcomes were used: the random-effects model (using DerSimonian and Laird's method[17]) and the fixed-effects model (using Mantel-Haenszel's method[18]). Heterogeneity of included studies was estimated by both Cochran's *Q* statistic (*P*-value less than 0.10 was considered as statistically significant heterogeneity) and I^2 statistic (values of 25%, 50%, and 75% represent low, medium, and high heterogeneity, respectively)[19]. For Cochran's *Q* statistic, the results were pooled by using the random-effect model when $P < 0.10$, otherwise the fixed-effect model was used. Sensitivity analysis was performed by sequential omission of individual studies to investigate the influence of each individual study on the overall meta-analysis. Publication bias was investigated by Begg's funnel plot method, Egger's linear regression method, and Begg's rank correlation method[20]. All *P* values were two-sided.

RESULTS

Literature searching and data extraction

Totally 331 potentially relevant published articles were identified initially, including 231 articles from PubMed, 47 articles from WanFang database, and 53 articles from CNKI database. According to the literature selection criteria as shown in ***Fig. 1***, duplicate articles (n = 24) or studies failed to meet other eligibility criteria (n = 289) were excluded. Finally, 18 eligible articles were included in this meta-analysis[21–38].

Table 1 **Characteristics of *IL28B* rs8099917, rs12979860, rs10853728 and rs7248668 polymorphisms' genotype distributions in studies included in the meta-analysis.**

						Genotype for SVR			Genotype for NR	
IL28B polymorphism	No.	Reference	HCV genotype	No. of patients	No. of SVR	TT(CC/CC/GG)	TG/GG(CT/TT; CG/GG;AG/AA)	No. of NR	TT(CC/CC/GG)	TG/GG(CT/TT; CG/GG;AG/AA)
rs8099917	1	Cai et al.	Multiple	84	65	62	3	19	15	4
	3	Gao et al.	1	97	63	55	8	34	24	10
	6	Lin et al.	1	191	131	123	8	60	47	13
	7	Xie et al.	Multiple	220	140	100	40	80	22	58
	10	Li et al.	1	56	34	31	3	22	14	8
	11	Ochi et al.	1b	44	25	21	4	19	9	10
			2a	29	25	24	1	4	2	2
	12	Guo et al.	1	126	58	26	32	68	17	51
			non1	110	73	60	13	37	17	20
	13	Yu et al.	2	482	429	386	43	53	46	7
	19	Hsu et al.	1,2	91	74	67	7	17	10	7
	23	Chen et al.	Multiple	728	559	517	42	169	135	34
	24	Yu et al.	1	528	392	354	38	136	73	63
rs12979860	1	Cai et al.	Multiple	84	65	62	3	19	14	5
	5	Xu et al.	Multiple	56	46	39	7	10	4	6
	6	Lin et al.	1	191	131	124	7	60	47	13
	15	Lv et al.	1	77	53	52	1	24	12	12
			non1	95	75	66	9	20	15	5
	18	Xie et al.	Multiple	220	140	100	40	80	22	58
	20	Liao et al.	Multiple	92	58	56	2	34	26	8
	23	Chen et al.	Multiple	728	559	521	38	169	133	36
rs10853728	6	Lin et al.	1	191	131	89	42	60	36	24
	13	Yu et al.	2	482	429	281	148	53	37	16
	23	Chen et al.	Multiple	728	559	377	182	169	93	76
rs7248668	1	Cai et al.	Multiple	84	65	62	3	19	15	4
	6	Lin et al.	1	191	131	123	8	60	48	12
	23	Chen et al.	Multiple	728	559	519	40	169	135	34

IL28B: interleukin 28B; HCV: hepatitis C virus; SVR: sustained virological response; NR: no response.

***Table 2* Characteristics of *MxA* rs2071430 and rs17000900 polymorphisms′ genotype distributions in studies included in the meta-analysis.**

MxA polymorphism	No.	Reference	HCV genotype	No. of patients	No. of SVR	Genotype for SVR		No. of NR	Genotype for NR	
						GT(CC/)	GT/TT(AC/AA)		GT(CC/)	GT/TT(AC/AA)
rs2071430	4	Huang et al.	Multiple	216	110	58	52	106	43	63
	8	Song et al.	Multiple	79	37	23	14	42	16	26
	25	Hu et al.	Multiple	46	32	20	12	14	4	10
rs17000900	4	Huang et al.	Multiple	216	110	35	75	106	49	57
	8	Song et al.	Multiple	79	37	17	20	42	29	13
	25	Hu et al.	Multiple	46	32	17	15	14	7	7

MxA: myxovirus resistance A; HCV; hepatitis C virus; SVR; sustained virological response; NR; no response.

The majority of current studies suggested that *IL28B* polymorphisms were related with treatment response in PEG-IFN/RBV therapy. ***Table 1*** shows the data extracted from the articles dealing with *IL28B* polymorphisms and PEG-IFN/RBV treatment response. Eleven articles, involving 2,069 cases with SVR and 718 cases with non-SVR, reported the association between *IL28B* rs8099917 and response to PEG-IFN/RBV treatment of HCV. Seven articles examined the association between *IL28B* rs12979860 and treatment response, including 1,127 cases with SVR and 416 cases with non-SVR. Three studies investigated the association between *IL28B* rs10853728 and treatment response, including 1,119 cases with SVR and 282 cases with non-SVR. Three articles reported the association of *IL28B* rs7248668 and treatment response, involving 755 cases with SVR and 248 cases with non-SVR.

MxA polymorphisms were also found to be related with SVR. As shown in ***Table 2***, three researchers examined the association of two *MxA* SNPs, *MxA* rs2071430 and *MxA* rs17000900, with PEG-IFN/RBV treatment response. Totally 179 cases with SVR and 162 cases with non-SVR were involved in these studies.

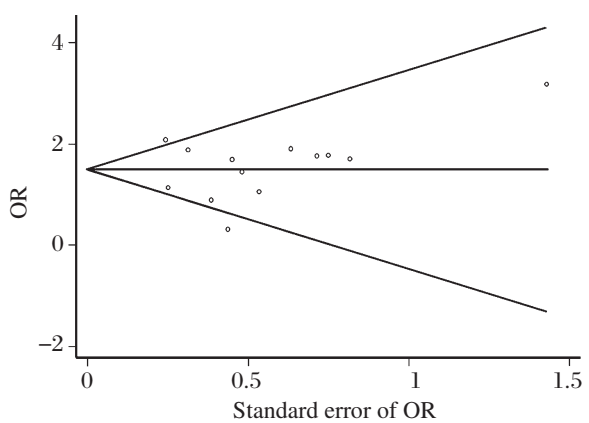

***Fig. 2* Publication bias among articles dealing with IL28B rs8099917.** Publication bias was evaluated by Begg′s funnel plot with pseudo 95% confidence limits. Each empty spot represents one publication.

Publication bias of included studies

As recommended, it was not necessary to evaluate publication bias when less than 10 articles were involved[39]. Therefore, publication bias was only evaluated among articles dealing with *IL28B* rs8099917 by Begg′s funnel-plot interpretation. As shown in ***Fig. 2***, no significant publication bias was found among those articles in Begg′s test ($P = 0.855$) and in Egger′s test ($P = 0.941$).

Meta-analysis results

Sensitivity analyses were performed to investigate the influence of each individual study on the overall meta-analysis (***Fig. 3A–3E***). For *IL28B* rs8099917, the between-study heterogeneity was significant when all 13 studies were pooled ($I^2 = 47\%$, $P = 0.03$), so random-effect model was used in subsequent analysis. To know the robustness of the result, we used both random-effect models and fixed-effect models in other cases.

The pooled results (***Fig. 4A***) showed that *IL28B* rs8099917 genotype TT was associated with higher SVR in PEG-IFN/RBV treatment compared with genotype GT/GG (OR=4.35, 95% CI: 3.10~6.12). In stratified analysis with different HCV genotypes, the results still indicated that rs8099917 TT genotype was associated with higher SVR ($OR_{genotype\ 1} = 4.59$, 95% CI: 2.82~7.47; $OR_{genotype\ non\text{-}1} = 3.81$, 95% CI: 1.02~14.29). There was no significant heterogeneity in virus genotype stratified analysis (genotype 1: $P = 0.13$, $I^2 = 42\%$; genotype non1: $P = 0.53$, $I^2 = 0\%$). Meta-regression analysis was also performed to investigate possible influence of viral genotype on heterogeneity. Studies by Cai *et al.*[21], Xie *et al.*[33], and Hsu *et al.*[38] were excluded for lack of data in meta-regression of HCV genotype covariants. There was no heterogeneity significance in HCV genotype (adjusted $R^2 = 24.61\%$, $P = 0.201$).

Fig. 4B shows that HCV patients with *IL28B* rs12979860 genotype CC had higher SVR than patients with genotype CT/TT in PEG-IFN/RBV treatment. The pooled OR from 8 studies was 5.37 (95% CI: 3.95~7.31). The pooled results from 3 studies showed that *IL28B* rs10853728 genotype CC was not significantly associated with SVR (OR = 1.32, 95% CI: 0.86~2.02; ***Fig. 4C***). Patients with *IL28B* rs7248668 genotype GG were also more likely to have SVR in treatment than patients with genotype AG/AA (OR = 3.50, 95% CI: 2.30~5.35; ***Fig. 4D***). Compared with genotype GG/TT, *MxA* rs2071430 genotype GT was an indicator of higher SVR (OR = 2.03, 95% CI: 1.31~3.13; ***Fig. 4E***). Patients with genotype GG were less likely to have SVR than patients with genotype GT/TT (OR = 0.30, 95% CI: 0.19~0.48). The results indicated that allele T had protective effect. *MxA* rs17000900 genotype CC was an indicator of negative treatment response. Compared with genotype AC/AA, genotype CC was less frequently found in patients with SVR (OR = 0.55, 95% CI: 0.35~0.85; ***Fig. 4F***).

DISCUSSION

Positive response to PEG-IFN/RBV therapy of HCV is affected by many factors. Host genetic variants have been indicated as predicators of SVR. *IL28B* and *MxA* are the most likely candidate genes. This current study summarizes the clinical data in Han Chinese popula–

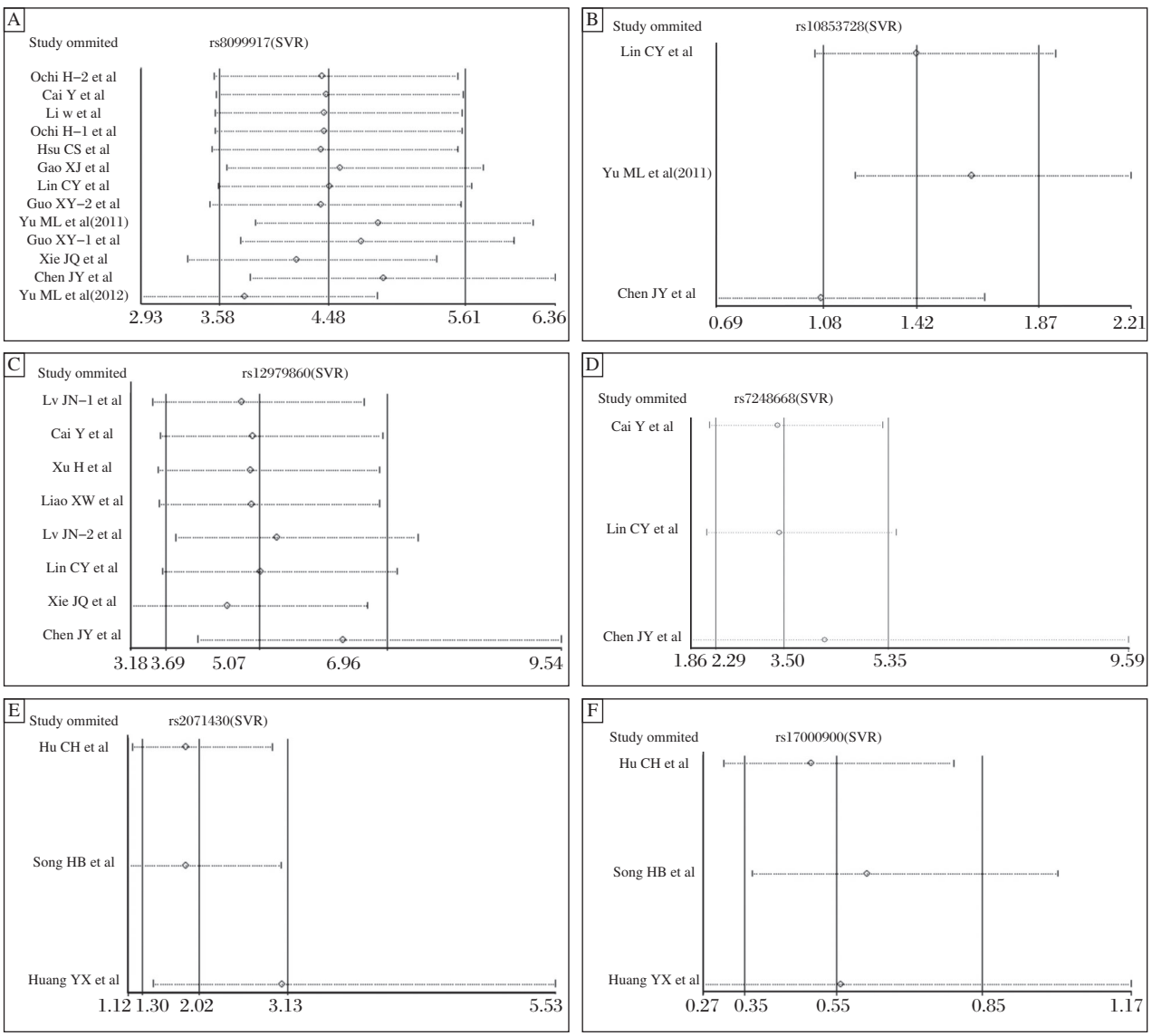

Fig. 3 **Sensitivity analyses for the SNPs.** Sensitivity analyses were carried out to investigate the influence of any one study on the overall meta-analysis by sequential omission of individual studies. ***3A*** to ***3F*** represent the sensitivity analysis for rs8099917, rs10853728, rs12979860, rs7248668, rs2071430 and rs17000900, respectively. Each small circle represents the OR value of the remaining studies when the corresponding study on the left side is omitted. SVR, sustained virological response.

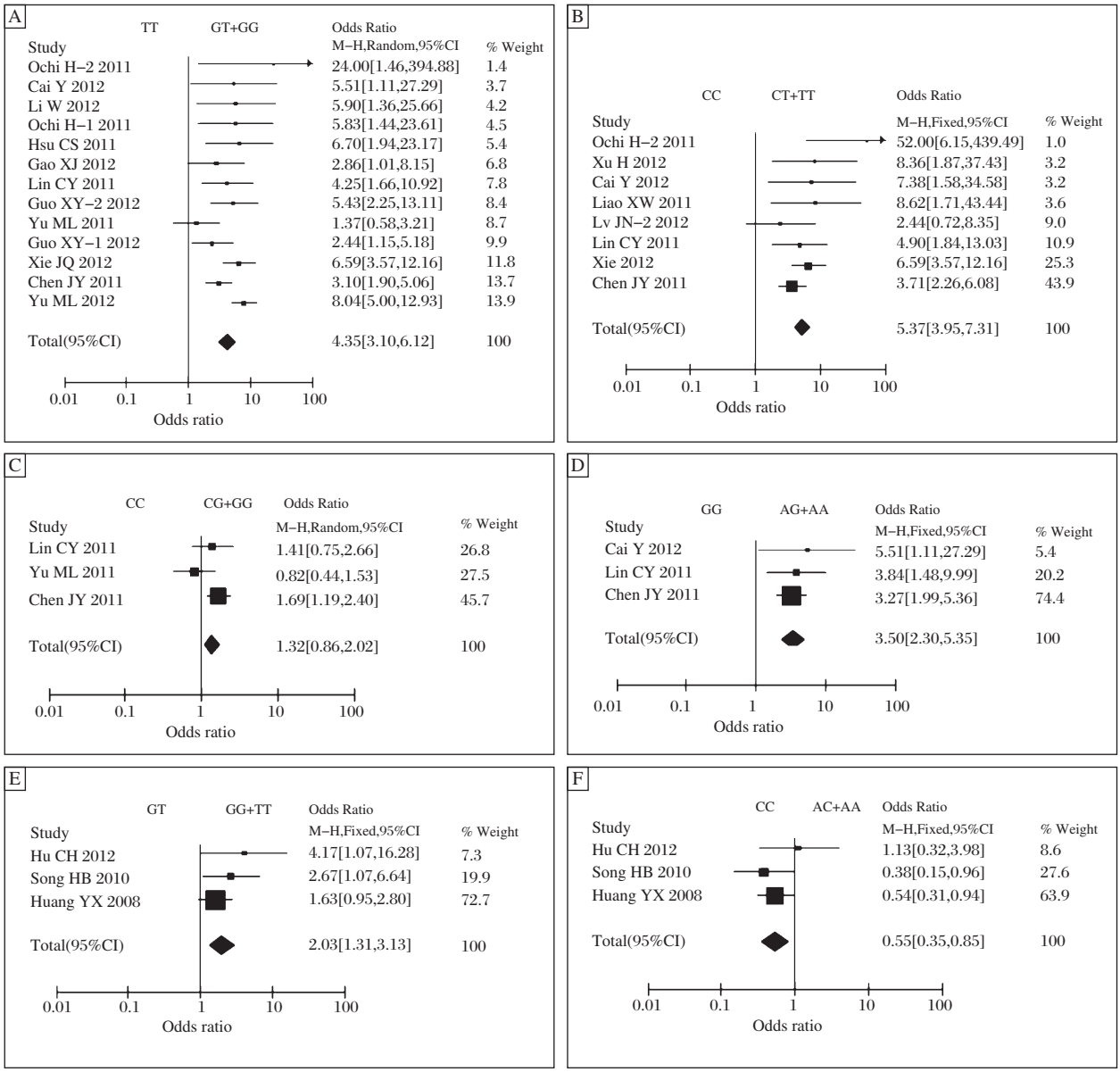

Fig. 4 **Forrest plots for association between the SNPs and response to PEG-IFN/ribavirin in HCV patients.** ***4A*** to ***4F*** represent the association between rs8099917, rs12979860, rs10853728, rs7248668, rs2071430, rs17000900 and response to PEG-IFN/ribavirin, respectively. The square represents the OR value of each study, and the weight of the square represents the sample size. The diamond represents the merged OR value. The segment represents 95% confidence level of OR. M-H indicates Mantel-Haenszel method; Fixed: fixed effect model; Random: random effect model; CI: confidence level; weight: the sample weight of each study.

tion. Our meta-analysis indicates that homozygote mutants of *IL28B* rs8099917 TT, rs12979860 CC, rs7248668 CC, and heterozygote of *MxA* rs2071430 genotype GT were associated with higher SVR, while homozygote mutants of *MxA* rs2071430 genotype GG and *MxA* rs17000900 genotype CC were associated with non-SVR. *MxA* rs2071430 and *MxA* rs17000900 are located within the IFN-stimulated response elements of the promoter region. Evidence shows that the *MxA* promoter sequence with T at -88 and A at -123 had about 4-fold higher activity in up-regulating the downstream reporter gene than that with C at -123 and G at -88[40]. The reported 3 SNPs of *IL28B* are located in the 5′ non-coding region. The variants in this region may also influence the expression of downstream genes and hence affect treatment response.

Virus genotype is also an important factor of SVR. SVR was usually easier to be achieved in those infected with HCV genotype 2/3 than those with genotype 1. However, our meta-analysis of *IL28B* rs8099917 showed no difference of SVR ratio between HCV genotype 1 and non-genotype 1. Due to lack of original data, we failed to do subgroup analysis of

HCV genotypes for other SNPs. It is understandable that most studies did not do subgroup analysis because HCV genotype 1 is the dominant strain in China. In most cases, the number of enrolled patients infected with HCV genotype 2/3 was not sufficient for stratified analysis.

The SVR rate is related with racial background. The frequency of SVR is usually higher in Asian patients than in European patients[41]. However, effects of some SNPs are universal. In addition to the studies in Asians, *IL28B* rs8099917 TT and rs12979860 CC also play a role in high SVR in Caucasians and Africans[12,13].

Some possible limitations should be noted in this meta-analysis. Firstly, only published studies were used for data extraction. Although the included articles all reported significant results, it is possible that negative results were obtained in some unpublished studies. Failure to include these negative results in the meta-analysis may over-estimate the association between the SNPs and treatment response. Secondly, the subjects from 18 included articles did not cover all areas of China, so the population may not be representative enough. Finally, the data quality differs among recruited studies. It was difficult to perform subgroup analysis of some confounding factors, including age, alanine transaminase, aspartate aminotransferase, viral load and liver fibrosis due to lack of original data or different grouping scales. Some studies did not have enough samples. In addition, most studies performed multiple comparisons with no bonferroni correction and increased the probability of type *I* error. As a matter of fact, we tested the data in some studies and the significance disappeared under bonferroni correction. Further studies are needed to provide more clinical data and to comprehensively evaluate the influence of host genetic variants on HCV treatment.

In conclusion, our findings suggest that host genetic variations are associated with virological response to interferon therapy of chronic HCV in Han Chinese patients

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