Two IL28B polymorphisms are associated with the treatment response of different genotypes of hepatitis C in different racial populations: A meta-analysis

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Abstract. The purpose of this present meta-analysis is to provide an accurate estimation of the association between two IL28B polymorphisms (rs8099917 and rs12979860) and sustained virological response (SVR) to standard treatment of patients of different racial descent infected with different genotypes of hepatitis C virus (HCV), and also to investigate the possible factors in the IL28B gene that contribute to the different SVR rates of patients with different subtypes of HCV infection across different populations. The electronic database PubMed was searched. Asian patients with a common homozygote (TT vs. TG/GG, OR=3.17; CC vs. CT/TT, OR=3.75) attained a higher rate of SVR, and a similar result was observed in European patients (TT vs. TG/GG, OR=1.74; CC vs. CT/TT, OR=2.50). Furthermore, HCV1-infected patients with a common homozygote (TT vs. TG/GG, OR=2.95; CC vs. CT/TT, OR=4.34) appeared to have a higher SVR rate than those with HCV2/3 (TT vs. TG/GG, OR=1.56; CC vs. CT/TT, OR=1.37). The frequency of the common homozygote in Asian patients was high, followed by European patients and African patients. In all, Asian patients attained a higher SVR rate than European patients ($P<0.05$). Patients with HCV1 infection had a lower SVR rate than those with HCV2/3 infection ($P<0.001$). Our results suggest that both the common allele frequency and racial descent itself contribute to the difference in SVR rates across different population groups, and the common allele frequency may partly elucidate the different SVR rates in patients with different genotypes of HCV.

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Introduction

Hepatitis C virus (HCV) infection has become a worldwide health problem (1). More than 170 million persons are infected with HCV. After HCV infection, more than 80% of infected patients progress to chronic hepatitis and other hepatic diseases (2). Pegylated-interferon (Peg-IFN) and ribavirin (RBV) combination therapy, which is the most effective initial therapy for viral clearance, has been recognized as a standard treatment for HCV infection. Unfortunately, this standard therapy produces sustained virological response (SVR) in only 50% of patients.

Many host and viral factors (3-5), particularly associated with racial descent, the genotype of HCV and variation in certain genes, influence the treatment response to Peg-IFN and RBV combination therapy. Recent genome-wide association studies (11-14) have shown that genetic variation (rs8099917 and rs12979860) in the IL28B gene is strongly associated with spontaneous clearance of HCV and treatment response to standard therapy in HCV-infected patients. In addition, previous studies (4,6,7) suggest that African-American ancestry is a powerful negative predictive factor for SVR. Moreover, patients with HCV1 infection were found to have a lower SVR rate than those with HCV2/3 infection (8-10). However, the association between IL28B polymorphisms and SVR to standard treatment in different racial populations or in patients infected with different genotypes of HCV has not yet been elucidated.

Ge *et al* (12) found that Asian patients have the highest C allele frequency at rs12979860, followed by European patients and African patients. The SVR rates across different population groups displayed a striking concordance with C allele frequency at rs12979860. This finding partly elucidates the differential treatment response in patients of different racial descent. However, is the common allele frequency the only reason for the different SVR rates across different population groups? It is still not clear whether racial descent itself contributes to the different SVR rates across different population groups. Moreover, previous studies (8-10) suggest that treatment with Peg-IFN and RBV results in a lower SVR

rate in patients with HCV genotype 1 (HCV1) than in patients with HCV genotypes 2 and/or 3 (HCV2/3). However, the inner factors, which contribute to this difference, are yet unclear. Therefore, an investigation of the polymorphisms of the IL28B gene may partly elucidate this difference.

The present meta-analysis was conducted to provide an accurate estimation of the association between the two polymorphisms and SVR to standard treatment in patients of different racial descent infected with different genotypes of HCV, and also to investigate the possible factors associated with the interleukin 28B (IL28B) gene that may contribute to the different SVR rates of patients with different subtypes of HCV infection across different populations. Notably, we found that both the common allele frequency and racial descent itself contributed to the difference in SVR rates across different population groups, and the common allele frequency may partly explain the difference in SVR rates in patients with different genotypes of HCV.

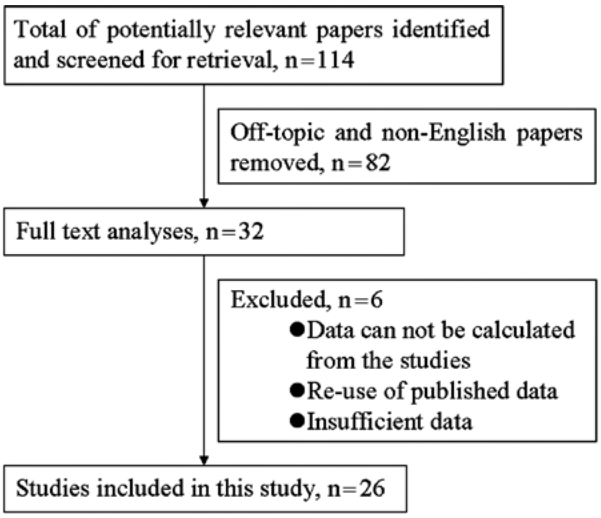

Figure 1. Study selection flow diagram.

Materials and methods

Literature search strategy. This meta-analysis was performed as described previously (15,16). The electronic PubMed database was searched (updated on March 30, 2011) using the following terms: IL28B and interferon λ3 (IFN λ3), combined with hepatitis C and HCV. Two reviewers (Wu and Wang) evaluated the titles and abstracts of the identified studies and references in the articles, and previous reviews for possible inclusion, respectively. Only studies published in English with full text articles were included in our study. The eligibility criteria included i) studies with available data to evaluate treatment success; ii) studies that examined the association between IL28B polymorphisms and treatment response of hepatitis C; iii) studies involving patients treated with standard therapy for HCV; iv) studies demonstrating treatment success based on an SVR, which was defined as undetectable HCV-RNA levels at 24 weeks post-treatment; v) studies with data that could be divided into an SVR group and non-SVR group; and vi) studies with sufficient and accurate data that could be extracted and calculated for estimating an odds ratio (OR) with 95% confidence interval (CI). For overlapping studies, only the study with the largest sample size was selected.

Data extraction. The following information was carefully extracted from the eligible studies independently by two reviewers (Wu and Wang): first author's name, year of publication, racial descent of the study population (categorized as Asian, European and African populations), number of different genotypes in the SVR group and non-SVR group, Hardy-Weinberg equilibrium (HWE) and genotype of HCV. Consensus was reached concerning all data by discussion.

Statistical analysis. Crude ORs with 95% CI were used to assess the association between IL28B polymorphisms and treatment response of hepatitis C. For meta-analysis of the association (case-control) studies, patients with SVR were considered as case patients, and patients without SVR were considered as control patients (17). Q statistics (18) was used to test the between-study heterogeneity. Between-study heterogeneity was considered to be significant at a P-value <0.10. When between-study heterogeneity existed, a random-effects model (the DerSimonian and Laird method) (19) was selected. Otherwise, the fixed-effects model (the Mantel-Haenszel method) (20) was used. Publication bias was tested by Funnel plots and Egger's linear regression (P<0.05 considered statistical significance). Fisher's exact test was used to compare the frequency of the genotypes at rs8099917 and rs12979860 in different patients. All analyses were performed using the software Stata version 11.0 (Stata Corporation, College Station, TX, USA).

Results

Eligible studies. Twenty-six studies (4,10,13,17,21-42) were included in this meta-analysis (Fig. 1). As shown in Table I, 16 studies (10,13,21-34) were eligible for examining the association between the IL28B polymorphism rs8099917 and treatment response of hepatitis C, including 3,540 cases with SVR and 2,208 cases with non-SVR. As shown in Table II, 17 studies (4,10,17,21,27-29,33-42) were eligible for examining the association between the IL28B polymorphism rs12979860 and treatment response of hepatitis C, including 2,951 cases with SVR and 2,506 cases with non-SVR.

Meta-analysis

Results of the association between IL28B polymorphism rs8099917 and treatment response of HCV. For rs8099917, patients with the TT genotype (2,819/4,106) had a higher rate of SVR than G allele carriers (721/1,642) from 16 studies (TT vs. TG/GG, OR=2.29, 95% CI 1.74-3.01, P<0.001 for heterogeneity). Of these 16 studies, seven (21,25,26,28,30-32) examined the association between IL28B polymorphism rs8099917 and the SVR rate in an Asian population, and the other nine in a European population. The SVR rate in Asian patients (2,160/3,426) was higher than that in European patients (1,380/2,322) (P=0.006). Compared to the non-TT genotype, Asian (TT vs. TG/GG, OR=3.17, 95% CI 2.15-4.68, P=0.003 for heterogeneity; Fig. 2) and European (TT vs. TG/GG, OR=1.74, 95% CI 1.22-2.48, P=0.005 for heterogeneity; Fig. 2) patients with the TT genotype both had a significantly

Table I. Characteristics of the studies included for the association between IL28B polymorphism rs8099917 and treatment response of hepatitis C.

Authors (Ref.)	Racial descent	Year	SVR		Non-SVR		P-value of HWE	HCV genotype
			TT	Non-TT (TG/GG)	TT	Non-TT (TG/GG)		
Suppiah *et al* (13)	European	2009	247	145 (130/15)	195	261 (227/34)	NA	1
Hayes *et al* (21)	Asian	2011	311	54 (51/3)	277	170 (148/22)	NA	1
Rauch *et al* (22)	European	2010	201	96 (86/10)	71	97 (85/12)	NA	1-4
Aparicio *et al* (23)	European	2010	56	11	48	45	>0.05	1,3,4; HIV
Grebely *et al* (24)	European[b]	2010	18	16 (13/3)	11	9 (9/0)	>0.05	1-4[a]
Yu *et al* (25)	Asian	2011	386	43	46	7	>0.05	2
Hsu *et al* (26)	Asian	2011	67	7 (7/0)	10	7 (7/0)	NA	1,2
Moghaddam *et al* (27)	European	2011	161	65 (59/6)	40	15 (14/1)	>0.01	3
Chen *et al* (28)	Asian	2011	517	42 (42/0)	135	34 (33/1)	<0.05	Multiple
Scherzer *et al* (29)	European	2011	29	24 (24/0)	10	6 (5/1)	NA	3
Sakamoto *et al* (30)	Asian	2011	81	17	19	12	NA	2
Lagging *et al* (10)	European	2011	54	34	43	37	<0.05	1
Kurosaki *et al* (31)	Asian	2011	173	20 (20/0)	172	131 (126/5)	NA	1
Kawaoka *et al* (32)	Asian	2011	372	70	180	66	NA	2
Bochud *et al* (33)	European	2011	47	16 (15/1)	6	3 (3/0)	>0.05	2,3
Sarrazin *et al* (34)	European	2011	99	61 (54/7)	24	21 (20/1)	>0.05	2,3

[a]Several patients were co-infected with HIV. [b]Most patients were European. NA, not available.

Table II. Characteristics of the studies included for the association between IL28B polymorphism rs12979860 and treatment response of hepatitis C.

Authors (Ref.)	Racial descent	Year	SVR		Non-SVR		P-value of HWE	HCV genotype
			CC	Non-CC (CT/TT)	CC	Non-CC (CT/TT)		
Mangia *et al* (35)	European	2010	82	119 (96/23)	18	49 (32/17)	>0.05	2,3
Hayes *et al* (21)	Asian	2011	311	55 (51/4)	271	175 (152/23)	NA	1
McCarthy *et al* (36)	European, African	2010	43	29 (22/7)	33	126 (99/27)	<0.05	1,2,3
Pineda *et al* (37)	European	2010	48	29 (19/10)	20	57 (47/10)	>0.05	1-4; HIV
Thompson *et al* (4)	European, African	2010	340	299 (239/60)	172	776 (559/217)	NA	1
Montes-Cano *et al* (38)	European	2010	68	45	34	72	>0.05	1-4
Honda *et al* (39)	Asian	2010	12	3 (3/0)	6	11 (10/1)	NA	1
de Araújo *et al* (40)	NA	2010	4	3	3	11	NA	1,3; HIV
Nattermann *et al* (17)	European	2011	83	89 (79/10)	54	122 (96/26)	>0.05	Multiple[a]
Darling *et al* (41)	European, African	2011	55	68 (51/17)	8	79 (52/27)	NA	1
Moghaddam *et al* (27)	European	2011	99	127 (105/22)	30	25 (24/1)	>0.01	3
Chen *et al* (28)	Asian	2011	521	38 (38/0)	133	36 (35/1)	>0.05	Multiple
Scherzer *et al* (29)	European	2011	19	34 (31/3)	6	10 (8/2)	NA	3
Reiberger *et al* (42)	European	2011	7	10	9	26	NA	1-4
Lagging *et al* (10)	European	2011	29	59	15	65	<0.05	1
Bochud *et al* (33)	European	2011	41	22 (18/4)	5	4 (4/0)	>0.05	2,3
Sarrazin *et al* (34)	European	2011	76	84 (51/33)	11	34 (15/19)	>0.05	2,3

[a]Several patients were co-infected with HIV. NA, not available.

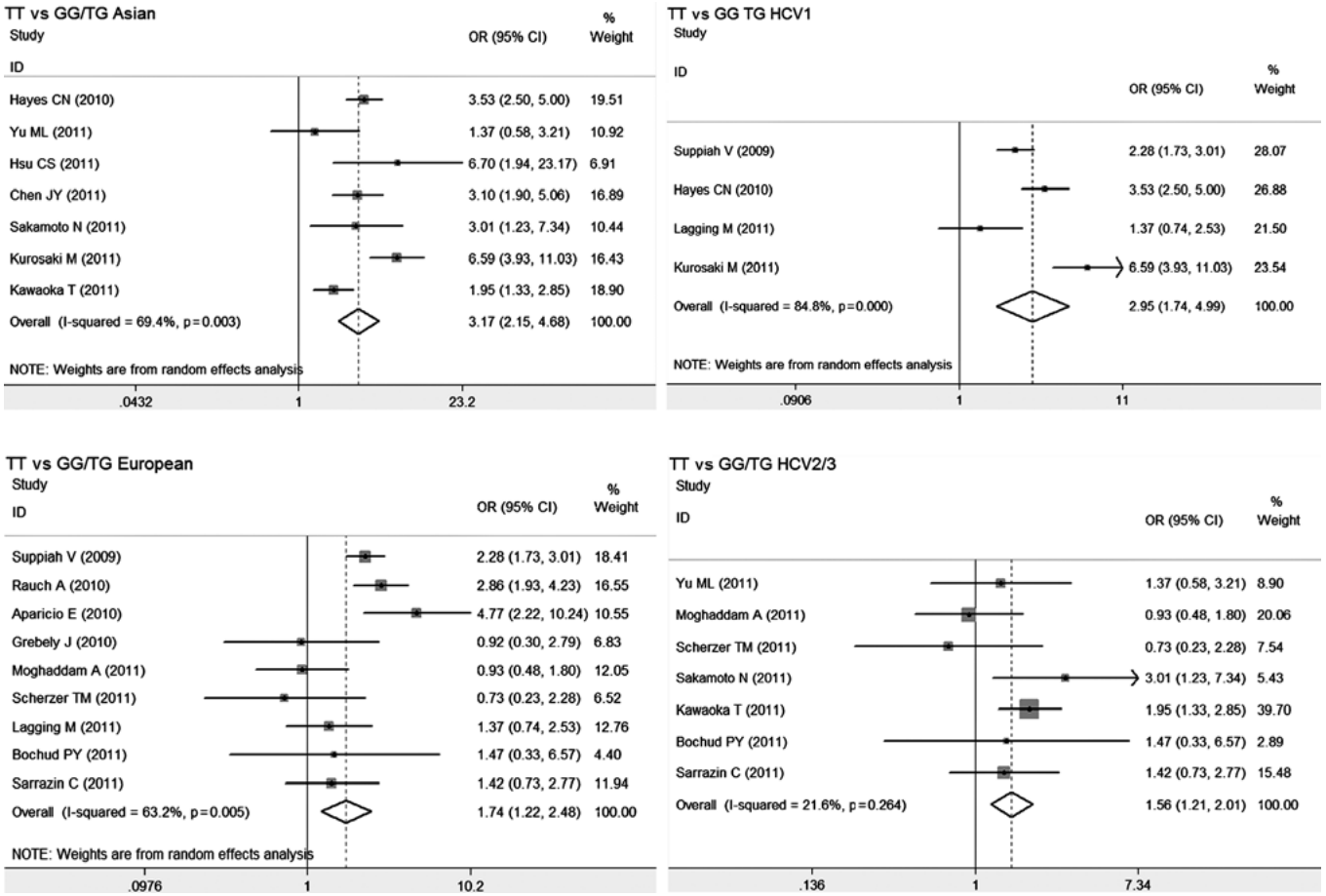

Figure 2. ORs of sustained virological response to anti-virus therapy in patients of different racial populations infected with different genotypes of HCV comparing the TT genotype with TG/GG genotypes of rs8099917.

higher SVR rate. Furthermore, the frequency of the TT genotype in Asian patients (2,746/3,426) was higher than that in the European patients (1,360/2,322) (P<0.001).

Of these 16 studies, four (10,13,21,31) were conducted to investigate the predictive value of IL28B polymorphism rs8099917 on the effect of standard therapy in patients with HCV1, and seven (25,27,29,30,32-34) in patients with HCV2/3. The rate of SVR to treatment in patients with HCV1 (1,038/2,324) was lower than in those with HCV2/3 (1,471/1,926) (P<0.001). Compared to the non-TT genotype, HCV1-infected patients with the TT genotype showed a significantly higher SVR rate (TT vs. TG/GG, OR=2.95, 95% CI 1.74-4.99, P<0.001 for heterogeneity; Fig. 2). Similar results were observed in the HCV2/3-infected patients (TT vs. TG/GG, OR=1.56, 95% CI 1.21-2.01, P=0.264 for heterogeneity; Fig. 2). Furthermore, the frequency of the TT genotype in patients with HCV1 (1,472/2,324) was less than than in patients with HCV2/3 (1,500/1,926) (P<0.001).

Results of the association between IL28B polymorphism rs12979860 and treatment response for HCV. This meta-analysis showed that patients with the homozygous CC genotype (1,838/2,666) had a significantly higher SVR rate for HCV than T allele carriers (1,113/2,791) (CC vs. CT/TT, OR=2.91, 95% CI 2.13-3.98, P<0.001 for heterogeneity). Of these 17 studies, three (4,36,41) examined the association between IL28B polymorphism rs12979860 and the SVR rate in an African population, three (21,28,39) in an Asian population and 13 (4,10,17,27,29,33-38,41,42) in a European population. The SVR rate was highest in the Asian population (940/1,572), followed by the European population (1,904/3,412) and African population (100/452) (P<0.001). Relative to T allele carriers, African patients with the CC genotype had the highest SVR rate (CC vs. CT/TT, OR=4.52, 95% CI 2.47-8.27, P=0.535 for heterogeneity; Fig. 3), followed by Asian patients (CC vs. CT/TT, OR=3.75, 95% CI 2.83-4.96, P=0.708 for heterogeneity; Fig. 3) and European patients (CC vs. CT/TT, OR=2.50, 95% CI 1.72-3.64, P<0.001 for heterogeneity; Fig. 3). Moreover, the CC genotype (59/452) at rs12979860 was less frequent in the African patients than that in the European (1,346/3,412) and Asian patients (1,254/1,572) (P<0.001).

Five studies (4,10,21,39,41) were conducted to investigate the predictive value of IL28B polymorphism rs12979860 on the effect of standard therapy in patients with HCV1, and five (27,29,33-35) in patients with HCV2/3. The rate of SVR to treatment in patients with HCV1 (1,231/2,809) was lower than that in patients with HCV2/3 (703/895) (P<0.001). Compared to T allele carriers, the HCV1-infected patients with the CC genotype (CC vs. CT/TT, OR=4.34, 95% CI 3.04-6.20, P=0.057 for heterogeneity; Fig. 4) appeared to have a higher rate of SVR compared to that of the HCV2/3-infected patients with the CC genotype (CC vs. CT/TT, OR=1.37, 95% CI 0.74-2.52, P=0.026 for heterogeneity; Fig. 4). Furthermore,

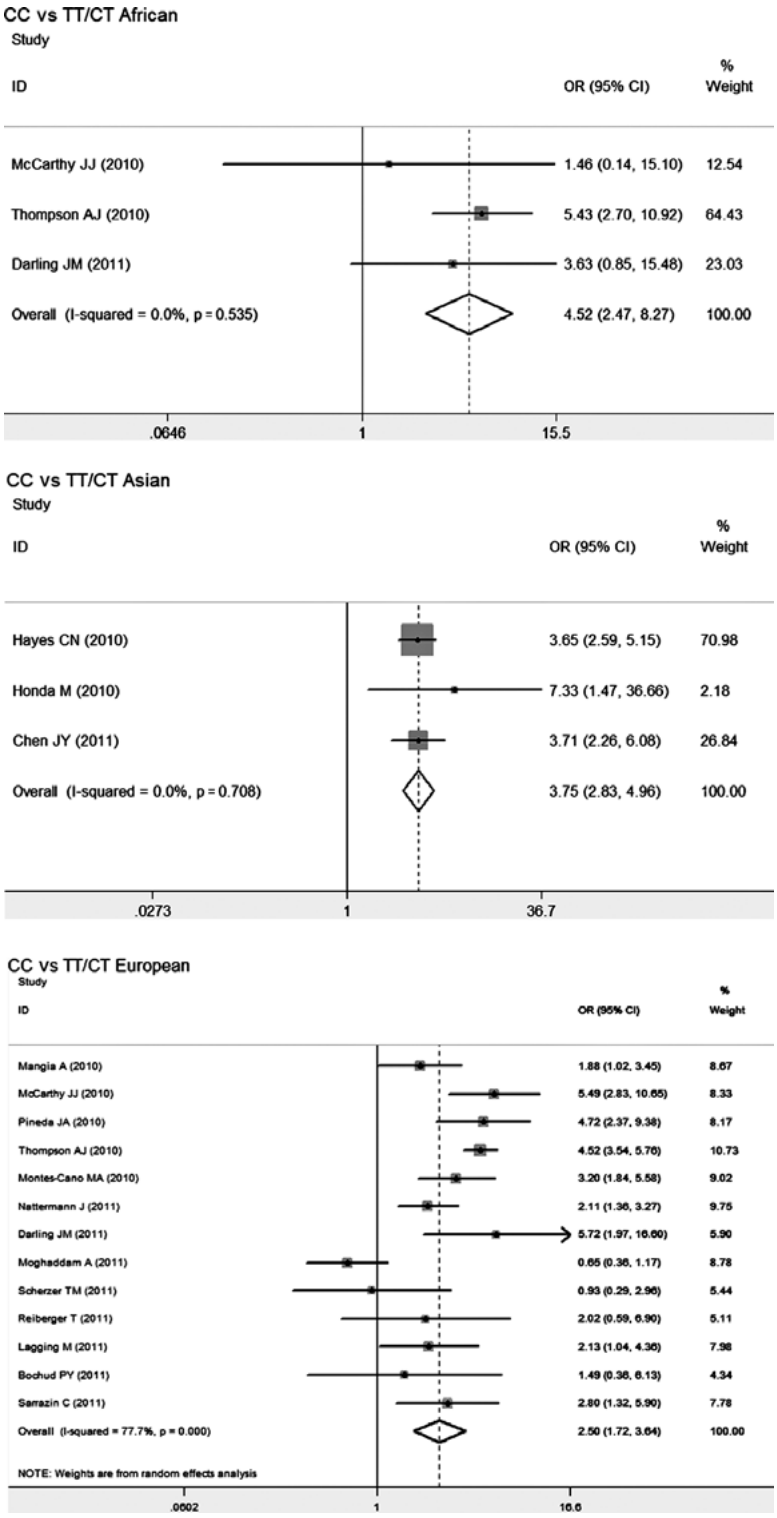

Figure 3. ORs of sustained virological response to anti-virus therapy in patients of different racial descent (African, Asian and European) comparing the CC genotype with the CT/TT genotypes of rs12979860.

the CC genotype in the HCV1-infected patients (1,219/2,809) was almost the same as that in the HCV2/3-infected patients (387/895) (P>0.05).

Co-expression of the *TT genotype at rs8099917 and CC genotype at rs12979860*. Patients with co-expression of the common homozygote TT genotype at rs8099917 and CC genotype at rs12979860 appeared to have a higher SVR rate than the rate in patients with the other genotypes. Data were obtained from only two studies (29,39). Patients with the common homozygote CC genotype at rs12979860 and the TT genotype at rs8099917 had a higher rate of SVR (30/42) than patients with co-expression of the rare homozygote TT genotype at rs12979860 and GG genotype at rs8099917 (0/2) and all other genotypes (38/57), but no significant difference was observed

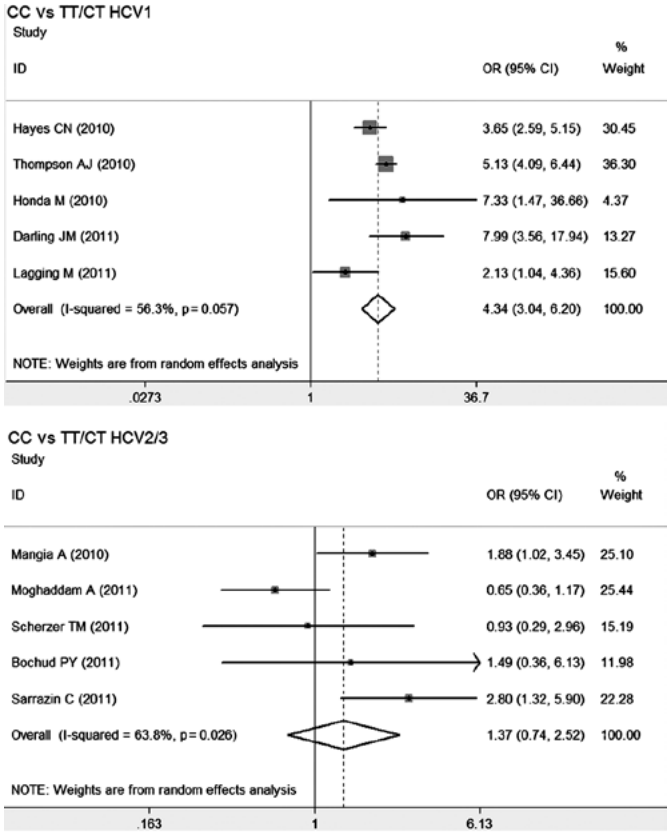

Figure 4. ORs of sustained virological response to anti-virus therapy in patients of different racial descent (African, Asian and European) infected with different genotypes of HCV (HCV1 and HCV2/3) comparing the CC genotype with CT/TT genotypes of rs12979860.

(P>0.05). More data are required to examine the association between co-expression of the TT genotype at rs8099917 and CC genotype at rs12979860 and treatment response to anti-HCV therapy.

Publication bias. Funnel plot and Egger's test were performed to assess the publication bias of studies which examined the association between IL28B polymorphisms (rs8099917 and rs12979860) and treatment response of hepatitis C. In the overall studies, no significant publication bias (P>0.05) was detected (data not shown).

Discussion

The present meta-analysis provides an accurate estimation of the association between the two polymorphisms and SVR to standard treatment in patients of different racial descent infected with different genotypes of HCV. The frequency of the common homozygote (TT genotype at rs8099917 and CC genotype at rs12979860) in Asian patients was higher than that in the European population. Furthermore, relative to the non-common homozygote genotype, Asian patients with the common homozygote appeared to have a higher SVR rate. Not only the frequency of the C allele at rs12979860 and T allele at rs8099917, but also the racial descent itself contributed to the high SVR rate in Asian patients. The SVR rate in patients with HCV1 was lower than that in those with HCV2/3. A low frequency of the common homozygote appeared to contribute to the low SVR rate in HCV1-infected patients. Further clinical trials should be carried out to confirm these significant findings.

The IL28B gene encodes IFN λ3 (43,44), whose polymorphisms are strongly associated with treatment response. Our study confirmed that the common homozygote of the two polymorphisms had a strong impact on SVR of HCV. IL28B polymorphisms provide useful pre-treatment stratification of patients for HCV treatment (12). We found that Asian patients with the common homozygote (TT genotype at rs8099917 and CC genotype at rs12979860) attained a higher rate of SVR when compared with European patients. Moreover, Asian HCV patients had a higher frequency of the common homozygote. Therefore, as demonstrated in previous studies (45,46), Asian HCV patients had a better response to treatment than European patients in this study. Ge *et al* (12) found that the SVR rates across different population groups displayed a striking concordance with C allele frequency. Our results suggest that not only the frequency of the C allele at rs12979860 and T allele at rs8099917, but also racial descent contributed to the different SVR rates across the different population groups. We found that African patients with the CC genotype had a higher SVR rate than T allele carriers. However, the the CC genotype at rs12979860 was far less frequent in African patients than in European and Asian patients in this meta-analysis. Thus, African patients still had the poorest response to treatment in accordance with previous studies (4,6,7).

Previous studies (8-10) suggest that treatment with Peg-IFN and RBV results in a lower SVR rate in patients with HCV1 than in patients with HCV2/3. The same result was observed in this meta-analysis. We found that HCV1-infected patients with the TT genotype had a higher rate of SVR compared to patients with HCV2/3. However, the frequency of the TT genotype at rs8099917 in HCV1 was lower than that in patients with HCV2/3 (P<0.001). Thus, the patients with HCV2/3 had a better outcome in our study.

Limitations did exist in the present meta-analysis. First, unadjusted ORs were obtained, and a more precise estimation may have be obtained adjusting according to age, gender, racial descent, genotype of HCV and variation in genes. Second, a deviation in HWE existed in several studies. However, the deviation, which may reflect a potential association between genotype and HCV infection, cannot be attributed to genotyping error (36). Third, several patients with HCV infection included in this meta-analysis were co-infected with HIV and/or HBV.

In conclusion, this meta-analysis found that patients with the common homozygote attained a higher rate of SVR to Peg-IFN and RBV combination therapy. Notably, we found that not only the frequency of the C allele at rs12979860 and T allele at rs8099917, but also racial descent contributed to the different SVR rates across the different population groups. Moreover, a low frequency of the common homozygote may contribute to a low SVR rate in HCV1-infected patients.

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