Role of gene polymorphisms in susceptibility to viral infections and drug response in human populations

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Certificate of Examination

This is to certify that the dissertation titled "**Role of gene polymorphisms in susceptibility to viral infections and drug response in human populations**" submitted by Ms. Suchitra S. Prabhu (Reg. No. MS14170) for the partial fulfilment of BS-MS dual degree programme of the Institute, has been examined by the thesis committee duly appointed by the Institute. The committee finds the work done by the candidate satisfactory and recommends that the report be accepted.

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Declaration

The work presented in this dissertation has been carried out by me under the guidance of Dr. Indranil Banerjee at the Indian Institute of Science Education and Research Mohali.

This work has not been submitted in part or in full for a degree, a diploma, or a fellowship to any other university or institute. Whenever contributions of others are involved, every effort is made to indicate this clearly, with due acknowledgement of collaborative research and discussions. This thesis is a bonafide record of original work done by me and all sources listed within have been detailed in the bibliography.

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In my capacity as the supervisor of the candidate's project work, I certify that the above statements by the candidate are true to the best of my knowledge.

Dr. Indranil Banerjee

(Supervisor)

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Notation

SNP, Single Nucleotide Polymorphism

IL28B, Interleukin 28B

HCV, Hepatitis C Virus

HIV, Human Immunodeficiency Virus

Peg-IFN, Pegylated Interferon

RBV, Ribavirin

SVR, Sustained Virological Response

RVR, Rapid Virological Response

ETR, End of the Treatment Response

ISG, Interferon Stimulating Gene

JAK-STAT, Janus Kinase- Signal Transducer and Activator of Transcription Proteins

DAA, Direct Acting Antiviral

OR, Odds Ratio

CI, Confidence Interval

IFITM3, Interferon Induced Transmembrane 3 Protein

IAV, Influenza A Virus

WHO, World Health Organisation

GWAS, Genome Wide Association Study

RNA, Ribonucleic acid

IBV, Influenza B virus

RT-PCR, Reverse transcriptase polymerase chain reaction

RFLP, Restriction fragment length polymorphism

HRM High Resolution Melting

NHC Normal human control

1000 G, 1000 Genomes Project

N M, Not mentioned

qPCR, Quantitative/ Real time polymerase chain reaction

RFLP, Restriction fragment length polymorphism

DNA seq, DNA sequencing

ND, not defined

Abstract

Chapter 1

HCV infection is of growing global concern due to high incidence of morbidity and mortality. Current therapy for chronic hepatitis C is based on a combination of peg-IFN and RBV given for 24-48 weeks based on the type virological response shown by the individual. Mostly, the medications are poorly tolerated and result in low response rates. It has been reported that SNP, in the IL28B gene may affect drug-response to the combined treatments of peg-IFN and RBV in HCV-infected patients, but the data were inconclusive. To resolve the controversy, we conducted a systematic meta-analysis to evaluate the role of SNPs present near to IL28B gene, rs12979860, rs8099917, rs12980275 and a dinucleotide variant ss469415590 in response to the dual drug therapy in HIV-HCV co-infected patients. We included 45 studies published before June 30, 2018 with a total of 9119 subjects (3992 cases and 5127 controls). OR and 95% CI were used to assess the strength of the association. Our results indicated a significant association of all the four polymorphisms considered with the SVR in all HCV genotypes of the HIV co-infected patients, receiving peg-IFN and RBV. The Odds ratio in the recessive models in rs12979860 was OR =3.26 [95% CI (2.77, 3.84)]; P<0.0001, rs8099917 with an OR = 3.78 [95% CI (2.81, 5.07)]; P<0.0001, rs12980275 with an OR = 2.96 [95% CI (2.22, 3.94)]; P<0.0001, and ss469415590 an OR = 3.50 [95% CI (2.37, 5.16)]; P<0.0001. Other genetic models like allele contrast, homozygote contrast, dominant model and additive models were also tested. Our results based on the subgroup analyses on HCV subtypes reveals that out of all HCV subtypes, the hardest to treat is HCV 1 following HCV 4 following HCV 2 and 3.In the case of rs12979860, CC genotype predisposes individuals to responding well with therapy, and ranges to individuals with CT, whereas the TT genotype predisposes them responding poorly with the therapy. Overall, our meta-analysis suggests a significant association of the IL28B gene polymorphisms rs12979860, rs8099917, ss469415590 and rs12980275 with the treatment response to peg-IFN and RBV in patients infected with HCV and HIV in the clearance of HCV as the treatment outcome.

Chapter 2

Influenza continues to be a major cause of morbidity and mortality worldwide and places a considerable socioeconomic burden on the society. Individual genetic variations affect the development and progression of many infectious diseases. The interferon induced transmembrane protein (*IFITM3*), as one of the key gene involved in the interferon pathway, known to be critical for defending the host against influenza virus and affecting disease susceptibility or severity. The rs12252 T>C variant in *IFITM3* is reported to be associated with susceptibility to influenza. However, the studies reported conflicting and inconclusive results. To resolve the controversy, we conducted a systematic meta-analysis to evaluate the role of the *IFITM3* rs12252 polymorphism in influenza susceptibility and severity, including twelve studies published before February 19, 2018 with a total 16,263 subjects (1836 influenza cases and 14,427 controls). OR and 95% CI were used to assess the strength of the association. Our results indicates, IFITM3 rs12252 polymorphism is associated with susceptibility to influenza for both severe and mild influenza with the allele contrast C vs. T: OR (severe) = 1.69, 95% CI = 1.23–2.33, P = 0.001, and OR (mild) = 1.46, 95% CI = 1.13–1.87, P = 0.004. Similarly, Individuals with CC genotype were found to be more susceptible to severe influenza than mild influenza infection. Subgroup analysis by ethnicity revealed that among White individuals, carriers of C allele are susceptible to both severe and mild influenza infection and East Asian individuals are more susceptible to severe influenza than mild influenza. Overall, our study suggests a significant association of the *IFITM3* rs12252 polymorphism with influenza in both the White and East Asian populations.

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Chapter 1

HIV-HCV Co-infection: An Evolving Epidemic

AIM: Studying the influence of IL28B gene polymorphisms on HCV clearance in HIV infected patients upon Peg-IFN and RBV treatment

1. Introduction

1.1 Basic Theory

It is estimated that HCV affects about 115 million people around the world out of which 2.3 millions are co-infected with HIV[1]. These are presently one of the most chronic viral infections and is significantly affecting morbidity and mortality. Chronic hepatitis infection gradually progresses to liver cirrhosis or hepatocellular carcinoma[2]. Patients co-infected with HCV and HIV have more liver damage than the HCV mono-infected ones, which is attributable to their similar route of transmission[3].

Current care for the hepatitis treatment includes an interferon (peg-IFNα) based therapy along with RBV. Standard dosage of the drugs include peg-IFNα, 180 mg/week, for 24 or 48 weeks plus a low-dose (800 mg/day) or standard weight-based dose (1000 or 1200 mg/day) of ribavirin[3,4]. The treatment aims in achieving enduring viral clearance or SVR or RVR. An undetectable HCV RNA concentration at the end of treatment and during 12 to 24 weeks of follow-up is defined as SVR and at week 4 is defined as RVR[4,5].Treatment outcomes in individuals with HCV 1 indicates only 40-50% of the cases showing SVR, 60% of the total in HCV 4 and over 80% in HCV 2/3 infection[6]. Ge *et al*., 2009 reported that patients of European ancestry have a significantly higher probability of being cured than patients of African ancestry[2].

This wide variability in treatment outcome suggests that there are additional factors involved in the virological responses in the patients such as host genetics. One such host factors known to be associated with the treatment response in HCV affected individuals is the allelic variants of *IL28B* which was independently reported by three Genome wide association studies[2,7,8]. IL28B gene product, IFN-λ-3 is an antiviral protein in humans which increases the cellular resistance by mediating the antiviral state of the cell during a viral infection. The IFN-λ acts through stimulating the Interferon stimulating genes (ISGs) via activating the JAK-STAT pathway. This happens when the Janus kinase signal transducer and transcription activator is activated by IFN-λ[6]. In diseased condition, the peg-IFN supplement when consumed exogenously, leads to native IFN-λ-3 secretion thus increasing the antiviral state of the cell. But some impairments in the IL28B gene can show differences in responding to the IFN therapy.

One such variant on the gene is the rs12979860 polymorphism, 3kb upstream of *IL28B*, shown to be associated with intrahepatic expression of ISGs which influences the treatment outcome. The unfavorable CT/TT genotype of rs12979860 exhibits higher ISG expression due to low activity of the endogenous IFN-λ and higher HCV replication ending up in poor response rate compared to the favorable CC genotype to the exogenous Peg-IFN and RBV treatment[9].

A case-control association study in patients of European and African ancestries infected with HCV 1 showed that rs12979860 is associated with an approximately two fold change in response to treatment, both among patients of European ancestry and African-Americans[2]. Tanaka *et al*., 2009 confirmed the same SNP and alongside reported a different one, rs8099917 to be strongly associated with SVR in a cohort of Japanese patients. Association analysis of haplotypes in that study identified seven other SNPs (rs8105790, rs11881222, rs8103142, rs28416813, rs4803219, rs8099917 and rs7248668) in the *IL28B* region suggesting association with response to PEG-IFNα and RBV treatment in the same cohort[7].

Although all the reported SNPs in the IL28B gene showed association with SVR to peg-IFN and RBV, rs12979860 was suggested as the critical predictor compared to the rest towards prediction of the treatment response[2,6,7]. But Franco *et al*.,2014 described an IFN-λ-4 ss469415590, a dinucleotide variant(TT or ΔG) situated upstream of IFN-λ-3 in the IL28B gene to be a better predictor of treatment response than rs12979860[10]. Since different studies suggested different estimates of the SNPs over the treatment response, due to various reasons such as variable sample sizes, HCV subtypes, treatment received etc, there is a need of further investigation to be done on impact of these SNPs on the treatment response.

Three GWASs investigated the role of rs12979860 with the treatment response, and thus achieving HCV clearance in HCV-HIV co-infected individuals[11,12].Sousa et al.,2013 showed that rs12979860, and on rs8099917 polymorphisms influence both the outcome of interferon treatment and the natural clearance of HCV 1 in HCV-HIV co-infected patients[11]. Rangnekar *et al*., 2012 also showed the association of rs12979860 with higher SVR rate in HCV genotype 1 patients co-infected with HIV whereas another GWAS by Jia *et al*., 2012 confirmed that rate of SVR in treatment-naive subjects infected with genotype 2 or 3 is 80.6%, higher than 48.5% in patients with HCV genotype 1 or 4 but with a limited number of studies[13]. All the studies had small sample size.

Since then, 38 case-control association studies have been published on clearance of HCV infection in HCV-HIV co-infected individuals upon Peg-IFN and RBV therapy[10,14–50]. We performed a systematic meta-analysis taking all eligible studies published till June 30, 2018 on three SNPs (rs12979860, rs8099917 and rs12980275) and a dinucleotide variant (ss469415590) present in *IL28B*, stratifying the data on the basis of HCV genotype present in the individual and on the type of treatment response ie., SVR or RVR to understand the association of the polymorphisms on HCV clearance in HCV-HIV co-infected individuals upon the therapy.

1.2 Materials and Methods

Study identification and selection of relevant studies

Articles investigating the association of the allelic variants rs12979860, rs8099917, rs12980275, and ss469415590 with treatment response of HCV in HIV infected patients when treated with Peg-IFN and RBV were shortlisted by conducting a literature search of the PubMed, Google Scholar and LibGen databases. The search was made extensive by adding relevant studies mentioned in the list of references given in studies on the above mentioned SNPs and treatment response. The terms "IL28B", "HIV", "HCV", "polymorphism", "SNP", "RBV", "peg-IFN", "rs12979860", "rs8099917", "ss469415590", "rs12980275" and "association" were used as search criteria in various combinations to screen for the studies. We retrieved a total of 336 records as of 30th June, 2018 from PubMed. Following the inclusion and exclusion criteria, we finally found 105 studies. These were further screened for case–control association studies according to our inclusion and exclusion criteria and ended up in a total of 45 studies[5,10,14–56].

Study selection criteria

Inclusion criteria:

1. The study was communicated in English.
2. It examined the association between the IL28B polymorphisms rs12979860, rs8099917, ss469415590 and rs12980275 and HCV clearance in HCV-HIV co-infected patients treated with peg-IFN and RBV.
3. The study was performed on humans.
4. The design of the study was either case-control or cohort.
5. Genotypic frequencies and allelic frequencies for both cases and controls in the treatment responses evaluated (SVR and RVR) were available.
6. HCV infection in the affected was confirmed by PCR/RT-PCR for viral genome.

Exclusion criteria:

1. Studies with insufficient data for genotypes and alleles.
2. Data from abstracts, editorials, and review articles.
3. Animal studies.
4. Studies on family or sibling pairs rather than general population.
5. Studies having HCV or HIV mono-infection.
6. Studies including form of the disease except chronic HCV.
7. Treatment regimens other than peg-IFN and RBV if used in the diseases individuals.

Data extraction

Information regarding name of the first author, year of publication, place of study, gender, median age, genotyping methods, HCV subtypes present, type of virological response shown, polymorphisms present, number of cases and controls, type of control population, and the genotype and allele distributions were extracted from the studies.

Statistical analysis

A meta-analysis was performed for different genetic models to study the impact of both allele and genotype (i.e., allele contrast, homozygote contrast, dominant, recessive and additive models) on association of the different polymorphisms (rs12979860, rs8099917, ss469415590 and rs12980275 on drug response in HCV-HIV co-infected individuals. The subgroup analyses based on HCV subtypes, HCV 1,3,4 and 1/ 4 and 2/3 and type of virological response, SVR or RVR were also performed based on the available data. A random effect model based on DerSimonian and Liard method was used for sensitivity analysis and strength of association was evaluated by calculating the ORs along with the 95% CI for the genetic contrast models tested[57]. The pooled ORs for the fixed-effects model was calculated by the Mantel-Haenszel method[58,59]. Significance of the association was decided on the basis of *P* value keeping the statistical significance at $P < 0.05$.

Cochran's $\chi 2$–based Q statistic tests (considered statistically significant with $P<0.10$) were used to compare experimental interventions within option choices and the I^2 metric (where $I^2 = (Q - df)/ Q$) was used to quantify the heterogeneity. The I^2 metric is is independent of the number of studies and can be used to compare studies of different sizes using different types of outcome data. I^2 values in the range 0–25%, 25–50% and 50–75% denote low, moderate and high heterogeneity respectively[60]. The publication bias was assessed by the Eggers's linear regression test for funnel plot asymmetry and the Begg-Mazumdar test, based on Kendell's tau[61–64]. The statistical software StatsDirect (version 3.1.18) was used to analyze the data.

2. Summary and Conclusions

2.1 Concluding Remarks

A total of 3992 case and 5127 controls were considered in the whole study (refer Table 2 for number of cases and controls in case of each SNP). The procedure of data selection for this meta-analysis is summarized in Fig. 1. The SNPs studied are rs12979860 on which 36 case-control association studies that was reported was included[5,10,15–36,38,38–42,44–46,52,53,55,56]. In case of other polymorphisms, 6 studies on rs8099917[14,15,17,38,43,50], 4 studies on rs12980275[47–50] and 3 studies on the double nucleotide variant ss469415590[10,18,19] were included. Stratification for the subgroup analyses was done on the basis of HCV subtypes (HCV 1, 3, 4, 1/4, 2/3) and type of virological response shown (SVR or RVR).
Meta-analysis revealed that the rs12979860, rs8099917, rs129780275 SNPs and the ss469415590 dinucleotide variant, showed significant association with all the HCV subtypes taken together and tested for viral clearance on the Peg-INF and RBV therapy.

Association of rs12979860 C allele was tested using allele contrast model, showed association with the sustained virological response with an OR (allele contrast)=2.33 [95% CI (1.97, 2.77)]; P<0.0001, tested for genotype CC in homozygous contrast, dominant, recessive and additive genetic models, OR (homozygous contrast)= 4.75 [95% CI (3.14, 7.18)]; P<0.0001, OR(dominant) =2.54 [95% CI (1.73, 3.73)]; P<0.0001, OR (recessive) =3.26 [95% CI (2.77, 3.84)]; P<0.0001 and OR(additive) =2.33 [95% CI (1.83, 2.97)]; P <0.0001 also showed association. Though moderate to high heterogeneity was seen, no publication bias was present in the models. Similarly a significant association with the SNP was shown when tested for recessive model in patients showing Rapid virological response, OR (recessive) =2.48 [95% CI (1.59, 3.85)]; P<0.0001(refer Table 17 and Fig 4.1).
In the subgroup analysis based on HCV subtype, significant association was found between rs12979860 and response to the dual therapy treatment by Hepatitis C 1/4 type viral clearance. The recessive model showed statistically significant summary ORs signifying a considerable association of the CC genotype with obtaining both SVR and RVR with OR (recessive) =3.44 [95% CI (2.87, 4.12)]; P<0.0001, and OR (recessive) =2.86 [95% CI

(2.09,3.91)]; P <0.0001 respectively. The study on SVR was of moderate heterogeneity and on RVR was of low, whereas no publication bias was present in both the models. The allele contrast, homozygous contrast, dominant and additive models also showed statistically significant association in patients showing SVR with the Hepatitis C subtype 1/4 viral clearance on dual drug therapy with the rs12979860 SNP, OR(allele contrast) =2.43 [95% CI (2.04, 2.91)]; P<0.0001, OR(homozygous contrast)= 5.20 [95% CI (3.34, 8.10)]; P<0.0001, OR(dominant) =2.60 [95% CI (1.73, 3.93)]; P<0.0001 and OR(additive)=2.43 [95% CI (1.89, 3.13)]; P <0.0001. All models showed high heterogeneity and no publication bias(refer Table 17 anf Fig.4.2).When tested for people affected with HCV 2/3 subtype, no statistically significant association was found in people showing SVR nor RVR, OR (recessive) = 1.31 [95% CI (0.92, 1.88)]; P=0.1308, and OR (recessive) =1.04 [95% CI (0.28, 3.93)]; P=0.9502 respectively for SVR and RVR (refer Table 17 anf Fig. 4.4, 4.6).

In case of HCV 1 subtype, association was seen between rs12979860 and the HCV clearance rate in people who showed SVR and RVR in all the genetic models tested, OR(allele contrast, SVR) =2.48 [95% CI (1.95, 3.15)]; P<0.0001, OR(homozygous contrast, SVR) = 5.95 [95% CI (3.16, 11.19)]; P<0.0001, OR(dominant, SVR) =3.18 [95% CI (1.75, 5.76)]; P=0.0001, OR (recessive, SVR) = 3.06 [95% CI (2.37, 3.94)]; P<0.0001 OR (additive, SVR) =2.48 [95% CI (1.77, 3.48)]; P <0.0001 and OR (recessive, RVR) =2.97 [95% CI (2.09, 4.23)]; P <0.0001. Low heterogeneity was seen in all models, except recessive model in SVR which showed moderate heterogeneity, and no publication bias was detected in the models (refer Table 17 and Fig.4.5, 4.6).

No association on viral clearance with the polymorphism rs12979860 was found in people affected with Hepatitis C virus subtype 3, OR (recessive) = 1.16 [95% CI (0.58, 2.31)]; P= 0.673(refer Table 17 anf Fig.4.3).

HCV 4 subtype showed highest association till now seen with rs12979860 with the chance of Hepatitis clearance on dual drug therapy when tested with the recessive model on people

who showed sustained virological response, OR (recessive)= 10.22 [95% CI (4.99, 20.92)]; P<0.0001, with low heterogeneity and publication bias (refer Table 17 and Fig.4.4).

Hence, among all HCV subtypes, HCV 4 subtype affected patients with rs12979860 CC genotype when treated with peg-IFN and RBV stands a higher chance of clearance of hepatitis C when co-infected with HIV.

The second SNP studied was rs8099917 with favorable TT genotype showed statistically significant association with the viral clearance when all subtypes of hepatitis were considered together and also in a subgroup analysis with only Hepatitis C virus subtype 1/4 but no association was found in subgroup analysis of Hepatitis C virus 2/3 subtypes in people who showed SVR, OR (recessive, all HCV subtypes) = 3.78 [95% CI (2.81, 5.07)]; P<0.0001, OR (recessive, HCV 1/4) = 4.02 [95% CI (2.76, 5.86)]; P<0.0001 and OR (recessive) = 1.94 [95% CI (0.79, 4.76)]; P=0.1465. All models were of low heterogeneity and no publication bias was present in any (refer Table 17 and Fig.4.7).

The ss469415590 variant (TT or ΔG)occurring upstream of IL28B gene, earlier reported by Franco *et al.*,2014 to be a better predictor than rs12979860 of peg-IFN and RBV therapy in HCV-HIV co-infected patients, was also checked for all genetic contrast models including all HCV subtypes together and confirmed association of the variant with obtaining SVR. OR(allele contrast)=2.46 [95% CI (1.85, 3.28)]; P<0.0001, OR (homozygous contrast) = 4.77 [95% CI (2.49, 9.13)]; P<0.0001, OR(dominant) = 2.63 [95% CI (1.43, 4.86)]; P=0.0019, OR(recessive)= 3.50 [95% CI (2.37, 5.16)]; P<0.0001 and OR(additive)=2.46 [95% CI (1.65, 3.69)]; P <0.0001. All models were of low heterogeneity and no publication bias (refer Table 17 and fig.4.9).

Finally, association of hepatitis viral clearance was also checked with rs12980275 and found a significant association with attaining SVR in HIV co-infected patients on peg-IFN and RBV treatment, OR (recessive) = 2.96 [95% CI (2.22, 3.94)]; P<0.0001. Low

heterogeneity was seen along with no publication bias in the tested model (refer Table 17 and fig.4.8).

Our study suggests that, out of all HCV subtypes, the hardest to treat is HCV 1 following HCV 4 following HCV 2 and 3. The favorable genotype in clearance of HCV by treatment with peg-IFN and RBV in each polymorphism are rs12979860 CC, rs8099917 TT, rs12980275 AA and ss469415590 TT/TT. Individuals with these genetic variations showed better treatment response.

2.2 Future Outlook

Response guided therapy: People has been treated previously with peg-IFN and RBV but not necessarily each one will show a similar response. Some might and some might not have gotten cure or have got partially cured with the treatment. Hence it is important to know what kind of a failure they had on the treatment. Treatment response is a cue which will help us understand person-to-person variation upon receiving treatment, an important aspect of personalized medicine. Good responders to initial treatment can be cured with a shorter course of therapy.

Although all patients may have different genetic setup, subgroups of patients can share common mutations/changes which allows treatment to be designed for patient subgroups. Studying factors that will ease the way to decide treatment, and influence the viral replication or viral life cycle while in the host can help understand the patient condition better. IL28B is one such gene help optimize the treatment of patients with HCV, specifically in the context of HIV/HCV coinfection. Furthermore, small-molecule inhibitors of the HCV protease and polymerase have been developed, and pilot studies in humans have shown them to be highly potent at lowering levels of HCV RNA.It would be interesting to investigate whether IL28B polymorphisms also play a predictive role in these novel therapies and on other emerging drugs such as direct-acting antivirals (DAAs). More importantly, perhaps, they might act synergistically by both decreasing HCV replication and interfering with the ability of HCV to evade the mediators of IFN action. These combinations hold the promise of greatly improved rates of response to therapy of hepatitis C.

Chapter 2

Host Determinants of Influenza A Virus Infection

AIM: Studying the influence of IFITM3 rs12252 polymorphism on influenza susceptibility and severity

1. Introduction

1.1 Basic Theory

Influenza A Virus is a significant human pathogen causing recurrent seasonal epidemics, global pandemics and deadly zoonotic outbreaks. Global outbreaks such as the 2009 H1N1 in USA and Mexico, 1918 Spanish flu, 1957 Asian flu, 1968 Hong kong flu and the recent 2009 Swine flu have claimed millions of lives with immunocompromised populations being at particularly high risk[65]. The most effective measure of protection against influenza till now known are the seasonal vaccines, but due to the highly variable nature of the virus, emerging strains become drug resistive eventually decreasing effectiveness of the vaccines[66].

The severity of infection in each individual varies on the basis of their genetic profile[67]. The course of influenza infection and their severe progression is directed in a tug of war between viral and host genetic determinants. Understanding host genetic makeup, and virus infection mechanism can greatly improve strategies for antiviral therapies. Genetic case-control association studies have identified potential human gene variants, which can contribute to the severity of infection[67].

IFITM3, is an antiviral restriction factor which works at the endosomal level. It was described as a candidate gene which can be targeted in reducing the viral infection[68]. *IFITM3* belongs to class of genes induced by type I interferons. This transmembrane protein mediates the innate immune responses to infection by influenza A H1N1 virus, West Nile virus and Dengue virus, and the IFITM3 protein was defined as restricting the infection of cells with influenza A in an siRNA screen[69]. The rs12252 T>C polymorphism in this gene, a splicing site mutation, results in a truncated protein lacking 21 amino acids in the N-terminal domain as shown in Fig.1 from Kiselev *et al*, 2015 in the MIR journal which helps determining enhanced human susceptibility to pandemic influenza[69].

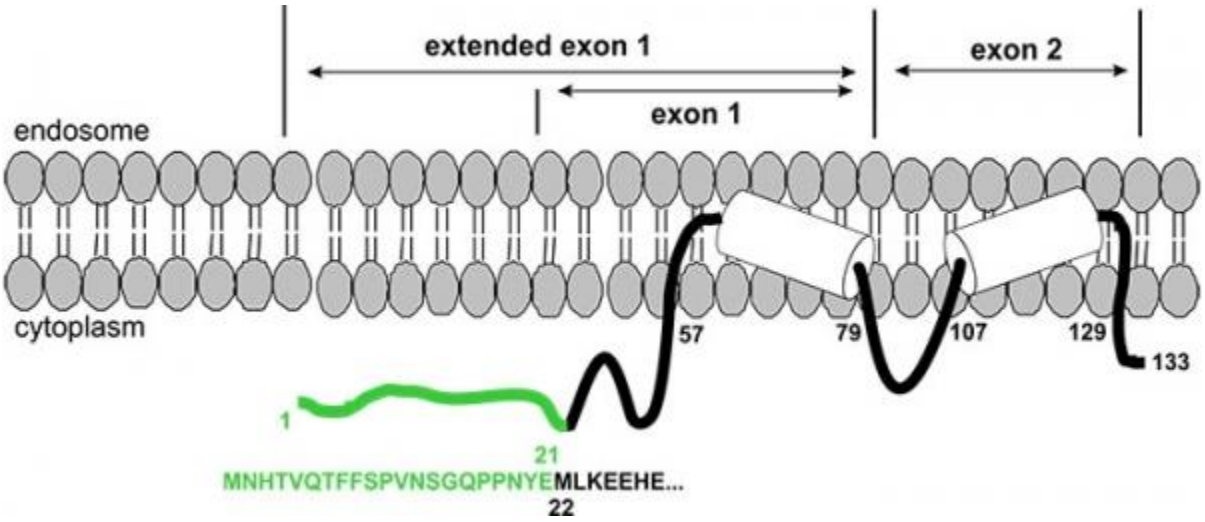


Fig. 1 Full length IFITM3 protein (the N terminal 21 amino acids which is missing in the truncated protein is colored green)[69]

IAV infection begins with the virus binding to host cell receptors. Following endocytosis by the clathrin-mediated endocytosis and macropinocytosis, the virus particles undergo membrane fusion at the late endosome, permitting their genomes, called the viral RNAs (vRNAs), to be released into the cytosol. The vRNAs are then transported to the nucleus, where they are transcribed and translated. The newly synthesized vRNAs and proteins are trafficked to the cell surface, where they are packaged into progeny virions[70]. The protein IFITM3 blocks the infection by preventing the entry of viral particles via endocytosis, It restricts the viral entry by blocking the fusion pore formation following virus-endosome

hemifusion, nevertheless, the detailed mechanisms of anti-viral defense formation in cells remain unknown[69]. Genome-wide microarray analysis revealed that p53 regulates the expression of IFITMs, so as to downregulate their expression during IAV infection[71]. In short, IFITM3 acts as anti-viral restriction factors and blocks influenza virus infectivity which could be depicted in Fig. 2 by Brass *et al*,2010 in the journal of Cell[72].

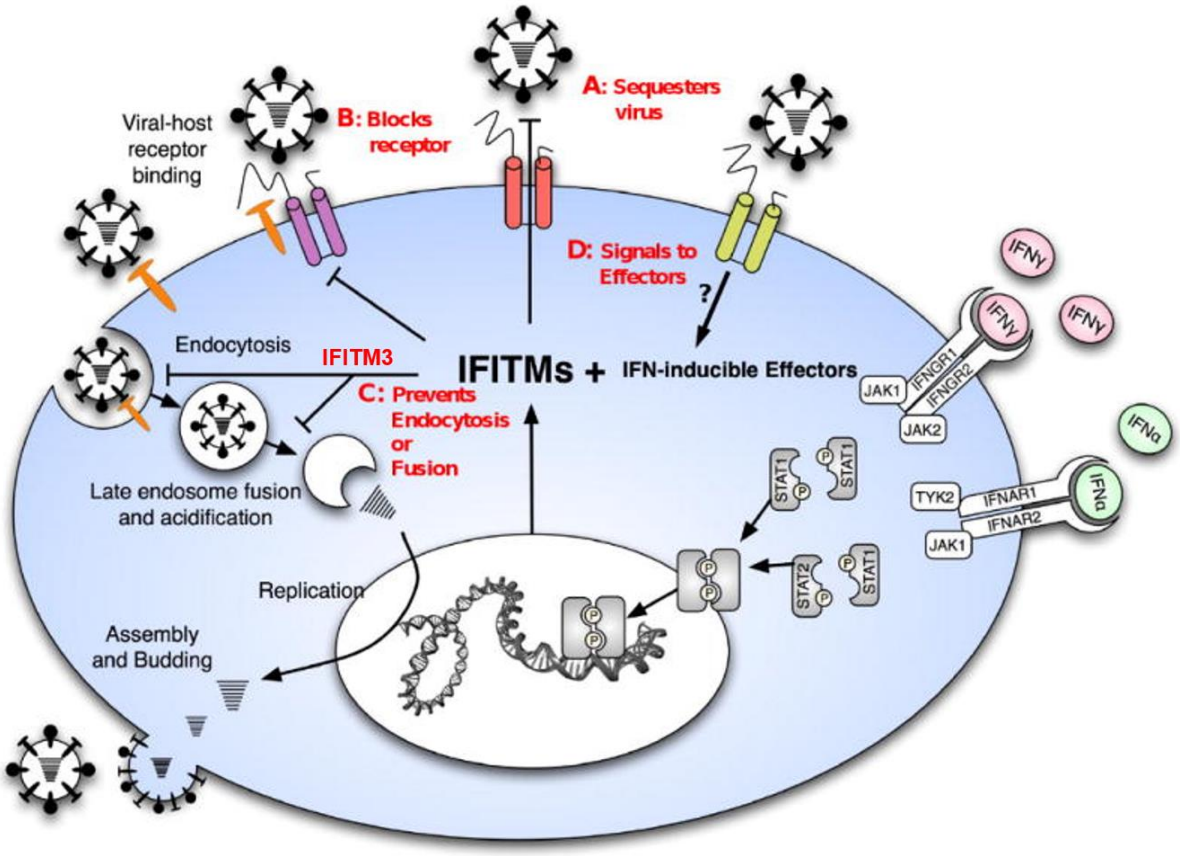


Fig. 2 A schematic of IAV life cycle depicting the role of IFITM3 in blocking viral endocytosis or fusion[72]

This effector molecule was shown to reduce influenza infection in a murine model, and the same study conducted a cohort study in a British population and showed that a minor allele, SNP rs12252-C, was significantly enriched in patients hospitalized due to H1N1/09 infection[68]. Another study, a Chinese population also revealed a selective advantage of this SNP in IFITM3 in resisting disease progression compared to the risk allele which had comparatively more number of cases[73]. Subsequent studies provided evidence of

association between the IFITM3 rs12252 polymorphism and influenza susceptibility and severity in different human populations[68,74–79]. However, other studies could not find any association of the T>C polymorphism in influenza[80–84] . Two meta-analysis independently evaluated the overall association between the above SNP and influenza susceptibility and severity with four studies included which was published from 2012 to 2014[68,78,79,84–86]. Since then eight more genetic association studies have been published[74–77,80–83]. Since these studies reported conflicting results, we performed an updated meta-analysis with greater statistical power to resolve the controversy.

In this study, we conducted a systematic meta-analysis to evaluate the role of the IFITM3 rs12252 polymorphism in influenza susceptibility and severity, including twelve studies published before February 19, 2018 with a total of 1836 influenza patients and 14427 healthy controls. We also examined the effect of the gene variant on the disease severity in two different ethnic populations: Whites (Europeans and people of European ancestry), and East Asians (Chinese).

1.2 Materials and methods

Study identification and selection of relevant studies

Articles investigating the association of IFITM3 rs12252 polymorphism with influenza susceptibility and severity were shortlisted by conducting a literature search of the PubMed, Google Scholar and LibGen databases. The search was made extensive by adding relevant studies mentioned in the list of references given in studies on rs12252 and influenza. The terms "IFITM3", "influenza", "association", "polymorphism", "SNP", and "rs12252" were used as search criteria in various combinations to screen for the studies. All the relevant studies published till February 19, 2018 were considered for initial screening. The articles were read in their entirety to evaluate the appropriateness for inclusion into this meta-analysis. Following the inclusion and exclusion criteria, we finally found 17 studies. These were further screened for case–control association studies according to our inclusion and exclusion criteria and ended up in a total of 12 studies[68,71,74–77,79–84].

Study selection criteria

Inclusion criteria:

1. The study was communicated in English.
2. It examined the association between the IFITM3 rs12252 polymorphism and influenza susceptibility and severity.
3. The study was performed on humans.
4. The design of the study was either case-control or cohort.
5. Genotypic frequencies for both the cases and controls were available.
6. Influenza in affected individual was confirmed by PCR/RT-PCR for viral genome.

Exclusion criteria:

1. Studies with insufficient data for genotypes and alleles.
2. Data from abstracts, editorials, and review articles.

3. Animal studies.
4. Studies on family or sibling pairs rather than general population.

Data extraction

A total of 339 potentially relevant studies up to February 19, 2018 were systematically identified using the keyword search in the electronic databases. After screening, seventeen studies were considered for further assessment[68,74–89]. Among them, one study was excluded as it was not relevant to the concerned SNP[87], two were already conducted meta-analysis[85,86], two studies were excluded for not having case-control or cohort study[88,89]. The rest twelve studies were included in our meta-analysis[68,74–84]. Information from the studies was extracted and segregated under the following categories: name of the first author, year of publication, study population, the strains of influenza viruses studied, severity, genotyping methods, number of cases and controls, type of control population, and the genotype and allele distributions. In cases where the allele frequencies were not provided, they were calculated on the basis of their genotype frequencies.

Statistical analysis

A meta-analysis was performed to examine the association of the IFITM3 rs12252-C with severe and mild influenza for the allele contrast, the contrast of homozygotes, and the recessive and dominant models.

All the tests performed in this meta-analysis followed the same procedure that of meta-analysis that was conducted in Chapter 1. Hence refer Pg. (Chapter1, 1.2 Materials and Methods, Statistical analysis).

2. Summary and Conclusions

2.1 Concluding Remarks

Table 18 shows the characteristics of studies included in the meta-analysis of IFITM3 rs12252 polymorphism in which a total of 1836 cases and 14,427 controls were considered for the analysis. Table 19 shows the distribution of the IFITM3 rs12252 genotypes and allele frequency in influenza patients and controls. Controls here are normal healthy population and some studies include data from the 1000 Genomes project (1000 G).The control group of Mehrbod *et al*,2017[77] did not follow the HWE.

A meta-analysis was performed to examine the association of the IFITM3 rs12252 T>C with severe and mild influenza for the allele contrast, the contrast of homozygotes, and the recessive and dominant models.

Meta-analysis reveals association of IFITM3 rs12252 T>C polymorphism with severe and mild influenza in the overall population as we can notice statistically significant ORs in the allele contrast models with both susceptibility to severe and mild influenza in the overall population in severe influenza with OR(severe) = 1.69 [95%CI(1.23-2.33)]; P = 0.0001, and OR(mild) = 1.46 [95%CI(1.13-1.87)]; P = 0.004 and similarly the other genetic models tested except for the recessive model in case of mild influenza which did not show significant association OR= 1.35 [95%CI(0.82-2.33)]; P = 0.240. Although low to moderate heterogeneity was present among the studies on severe influenza, there was publication bias. Similarly no inter-heterogeneity and no publication bias was present in the case of mild influenza (refer Table 20 and Fig. 6.1,6.2).

Studying the association between rs12252 polymorphism and the relative risk of influenza (severe vs. mild), although no association was found in allele contrast model OR = 1.47 [95%CI(0.82-2.63)]; P = 0.192 or dominant model OR = 1.19 [95%CI(0.77-1.85)]; P = 0.421, but significant association was detected in homozygote contrast OR = 4.69

[95%CI(2.16-10.17)]; P < 0.0001 and recessive model OR = 4.72 [95%CI(2.86-7.78)]; P < 0.0001. No publication bias and except for the allele contrast, no heterogeneity was detected in any of the genetic models tested.

Subgroup analysis by ethnicity showed significant association with severe influenza in case of the White population in the allele contrast, homozygote model and recessive model with OR = 1.35[95% CI (1.00-1.83)]; P = 0.048, OR = 9.92[95% CI (2.45-40.15)]; P = 0.001 and OR = 9.80[95% CI (2.42-39.62)]; P = 0.048 respectively but not in the dominant model OR = 1.18[95%CI (0.85-1.63)]. Though significant association was shown in case of the White population in mild influenza in the allele contrast and dominant model with OR = 1.48 [95% CI (1.11-1.97)]; P = 0.007 and OR = 1.43[95% CI (1.05-1.94)]; P = 0.021, that was not the case in the recessive model and homozygote model OR = 5.22 [95% CI (0.96-28.46)]; P = 0.056 and OR = 5.28[95% CI (0.97-28.78)]; P = 0.054. All publication bias data for the analyses are provided in Table 20.

Association of severe influenza susceptibility with the polymorphism tested, rs12252 of IFITM3 gene in East Asians showed significant association in all the genetic models tested (refer Table 20). Whereas mild influenza in case of East Asian population did not show any association with any of the genetic contrast.

Our results showed significant association of the IFITM3 rs12252 polymorphism with increased risk of severe and mild influenza in the overall population revealing a potential selective advantage for the SNP that may explain its high prevalence in certain human populations. Individuals with CC genotype are more susceptible to severe influenza than mild influenza infection. Stratified analyses by ethnicity revealed that the IFITM3 rs12252 polymorphism confers higher risk of severe and mild influenza to Whites (Europeans and people of European ancestry), whereas the East Asians (Chinese) are at higher risk of severe influenza only.

2.2 Future Outlook

Antiviral drugs are usually seen given as prescription drugs to shorten the severity and duration of the flu. But these existing drugs is eventually seen becoming ineffective due to the emergence of the drug-resistant viral strains.

Another way to circumvent this problem is to target the host cellular factors during viral entry and replication. Hence understanding influenza biology can help device novel strategies against the virus.

Genetic studies help us understand the susceptible genes as analyzing these genes gives us a clue on how they induce different kinds of response in different individuals. This can therefore be a stepping stone to personalized based medication and increasing the efficacy and safety of medications.

List of Figures

Fig. 3 Flow chart illustrating the study selection in Chapter 1

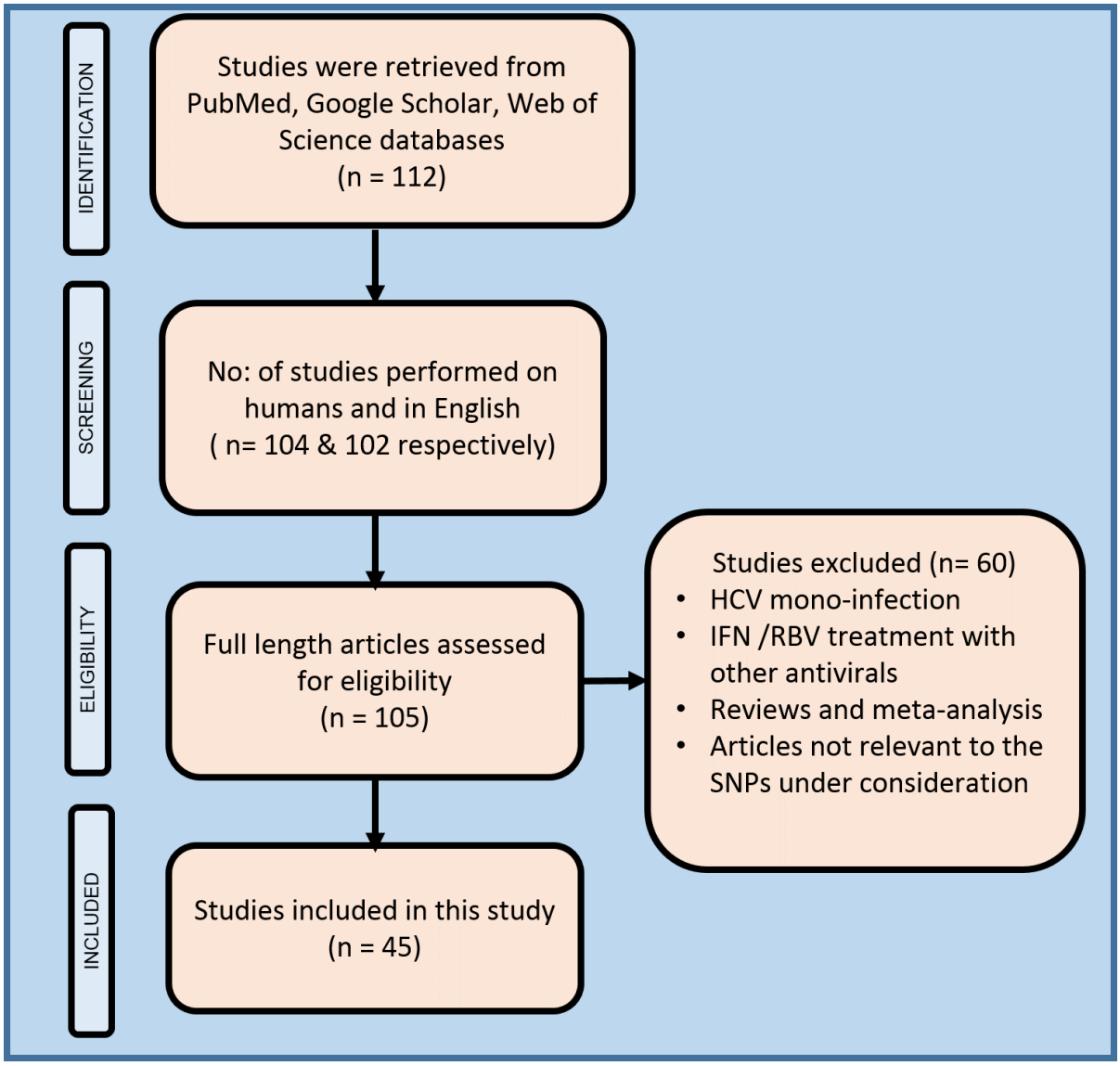
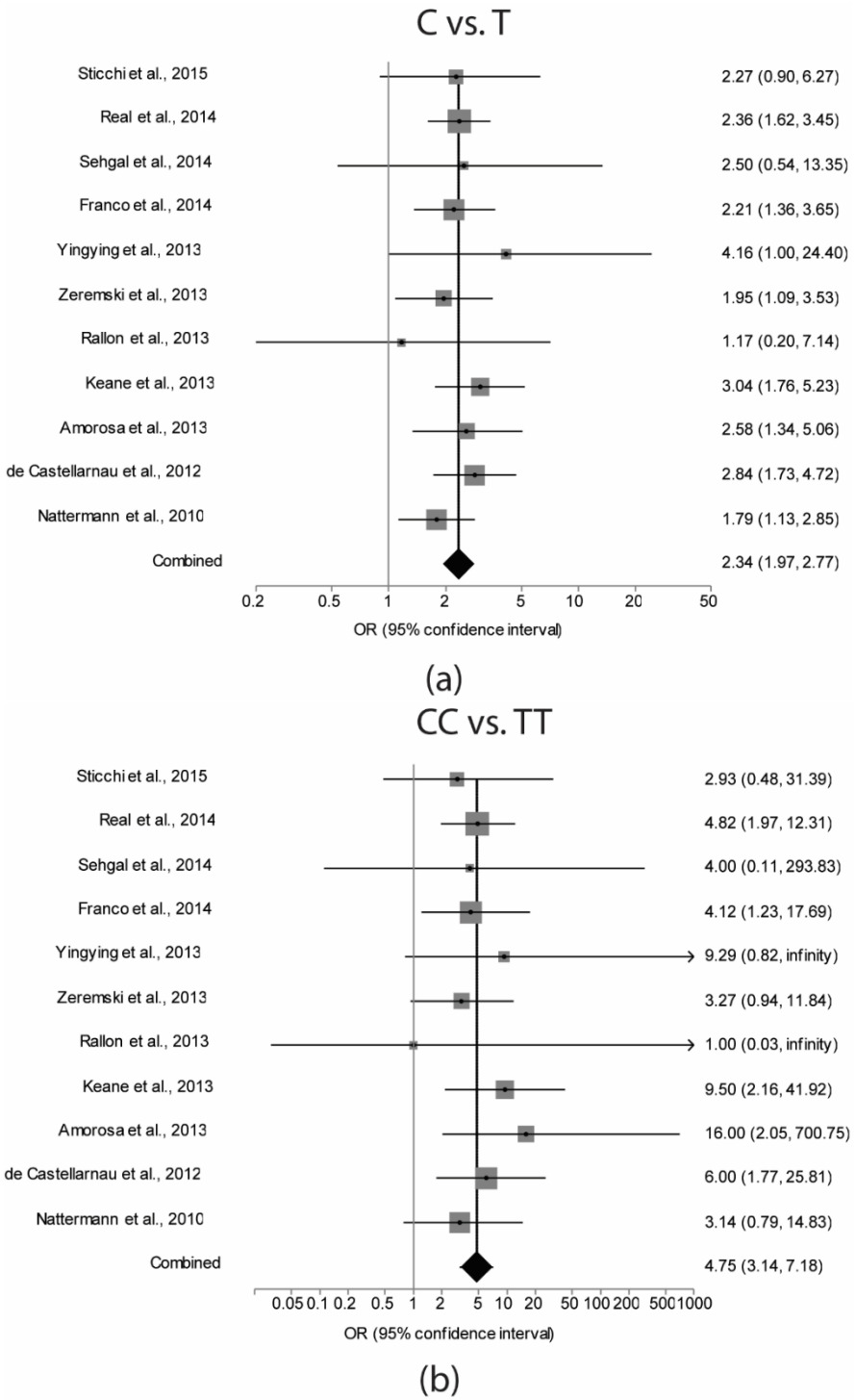
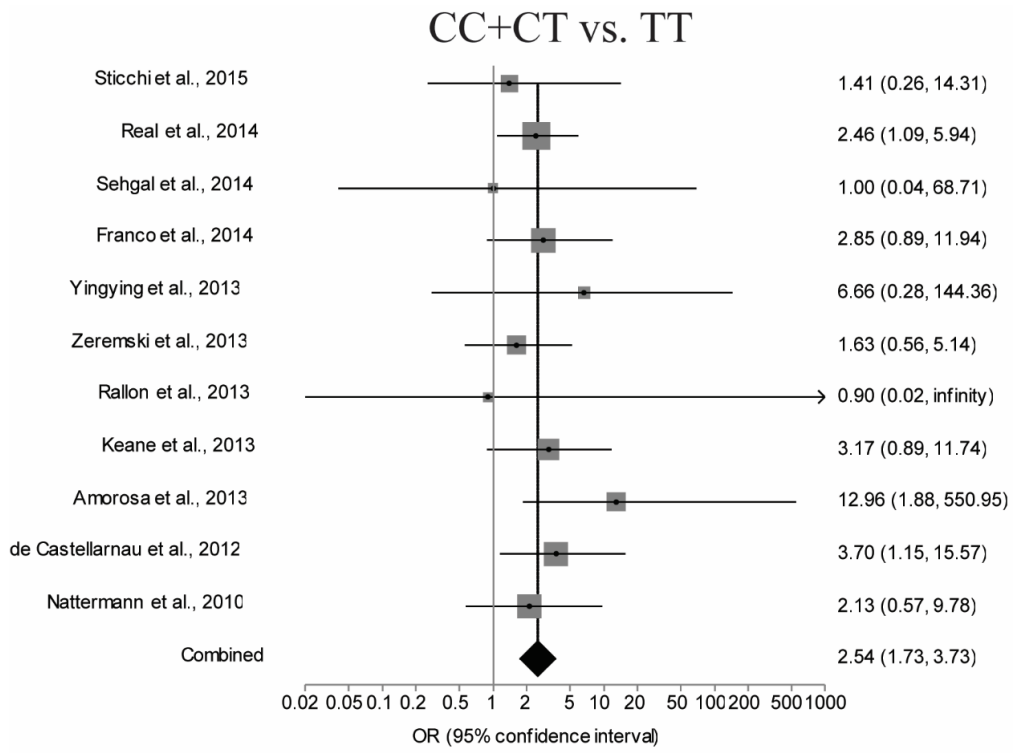
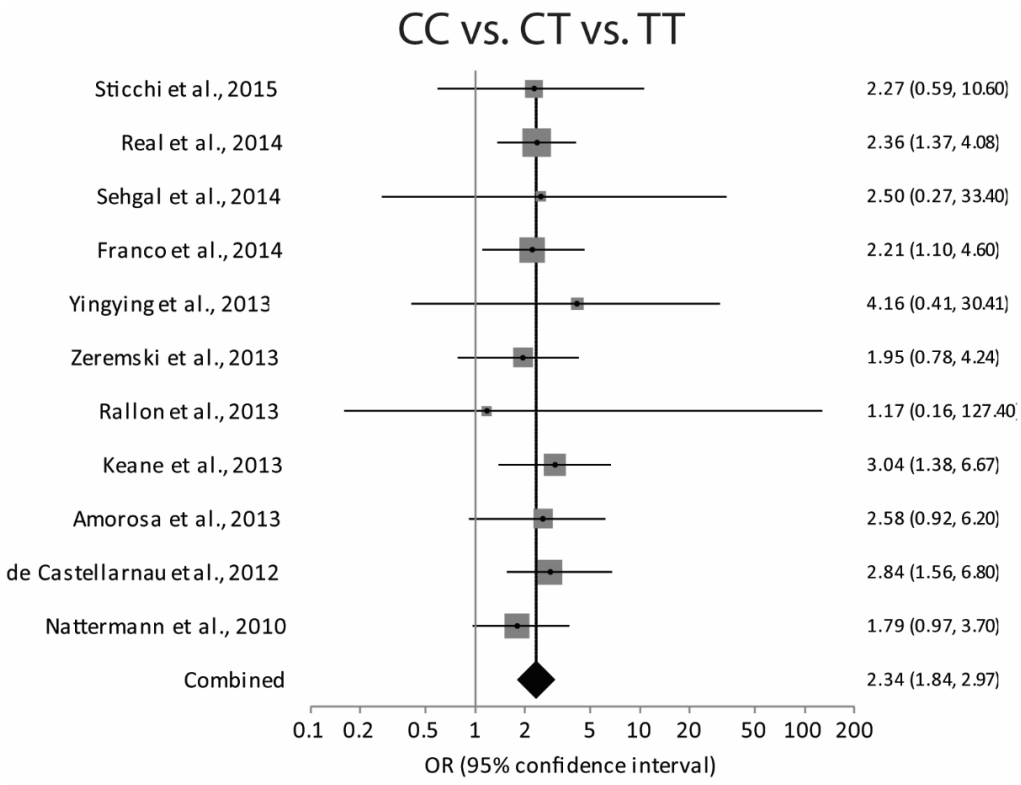


Fig. 4.1 The forest plots for the association between the *IL28B* rs12979860 polymorphism on SVR in all HCV subtypes taken together in the (a) allele contrast, (b) homozygote contrast, (c) dominant, (d) additive and (e) recessive genetic models.




CC+CT vs. TT
Sticchi et al., 2015
Real et al., 2014
Sehgal et al., 2014
Franco et al., 2014
Yingying et al., 2013
Zeremski et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
1.41 (0.26, 14.31)
2.46 (1.09, 5.94)
1.00 (0.04, 68.71)
2.85 (0.89, 11.94)
6.66 (0.28, 144.36)
1.63 (0.56, 5.14)
0.90 (0.02, infinity)
3.17 (0.89, 11.74)
12.96 (1.88, 550.95)
3.70 (1.15, 15.57)
2.13 (0.57, 9.78)
2.54 (1.73, 3.73)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200 500 1000
OR (95% confidence interval)

(c)


CC vs. CT vs. TT
Sticchi et al., 2015
Real et al., 2014
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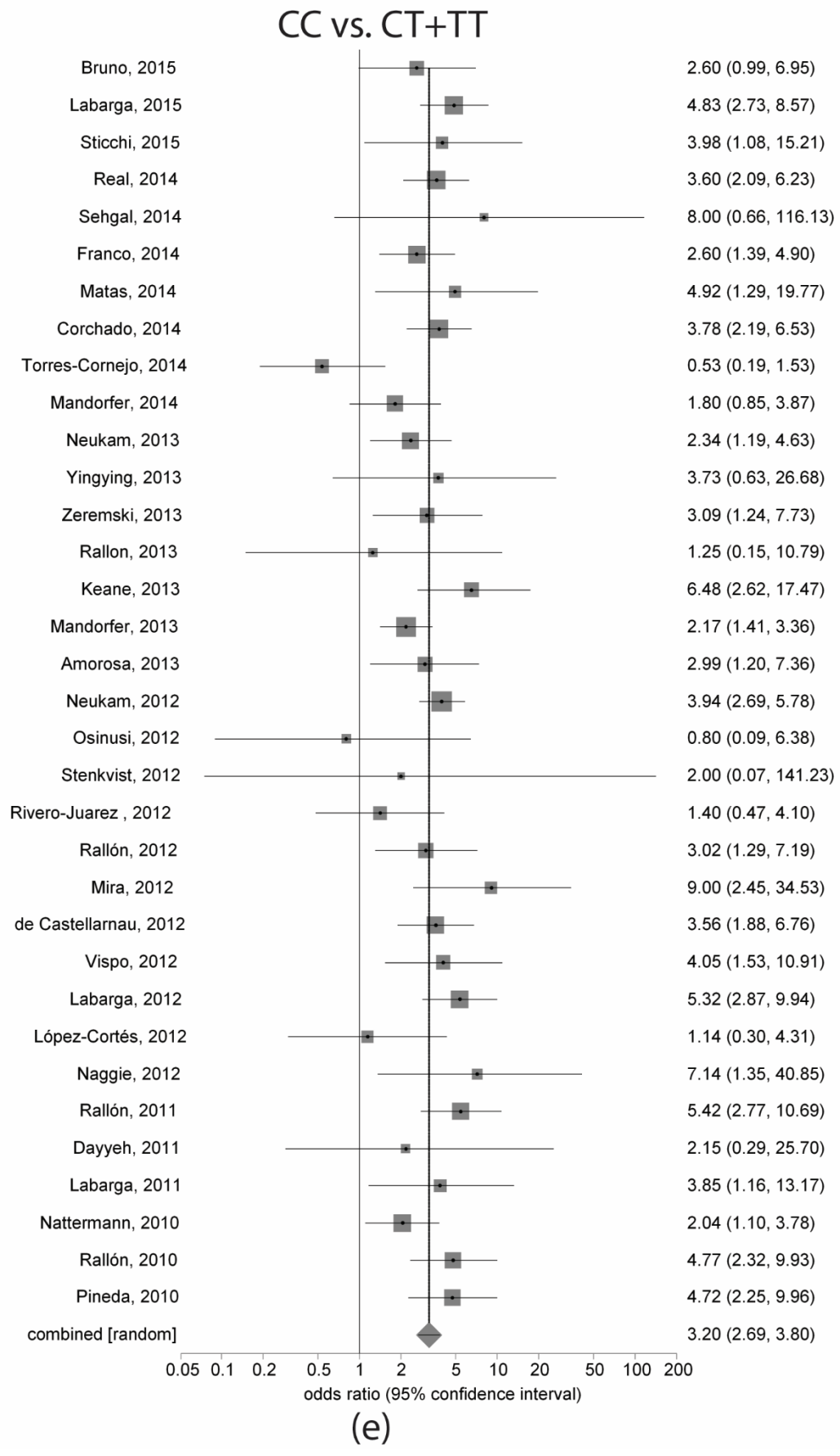
Franco et al., 2014
Yingying et al., 2013
Zeremski et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
2.27 (0.59, 10.60)
2.36 (1.37, 4.08)
2.50 (0.27, 33.40)
2.21 (1.10, 4.60)
4.16 (0.41, 30.41)
1.95 (0.78, 4.24)
1.17 (0.16, 127.40)
3.04 (1.38, 6.67)
2.58 (0.92, 6.20)
2.84 (1.56, 6.80)
1.79 (0.97, 3.70)
2.34 (1.84, 2.97)
0.1 0.2 0.5 1 2 5 10 20 50 100 200
OR (95% confidence interval)

(d)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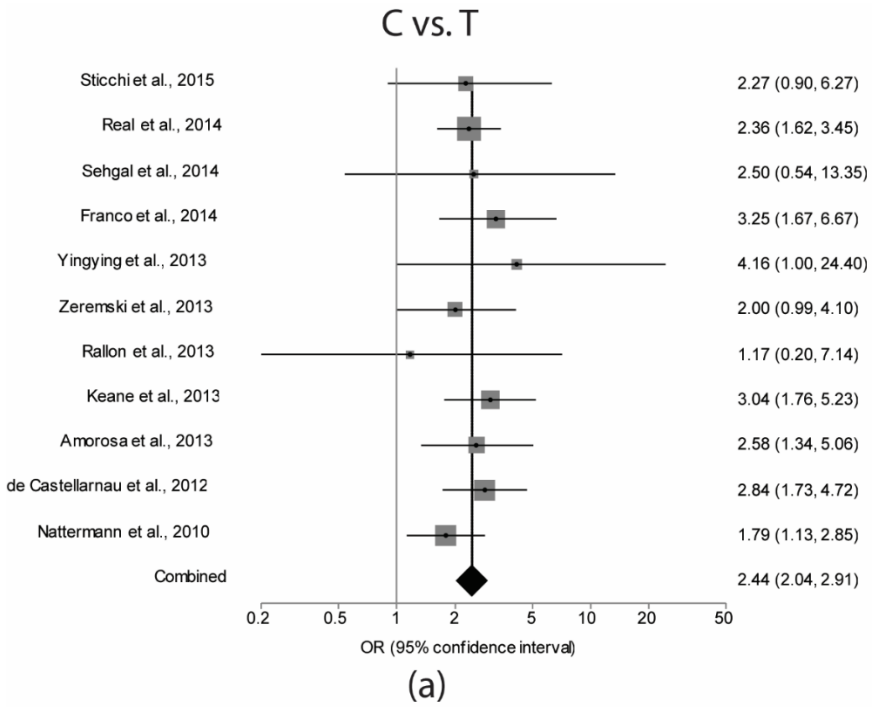
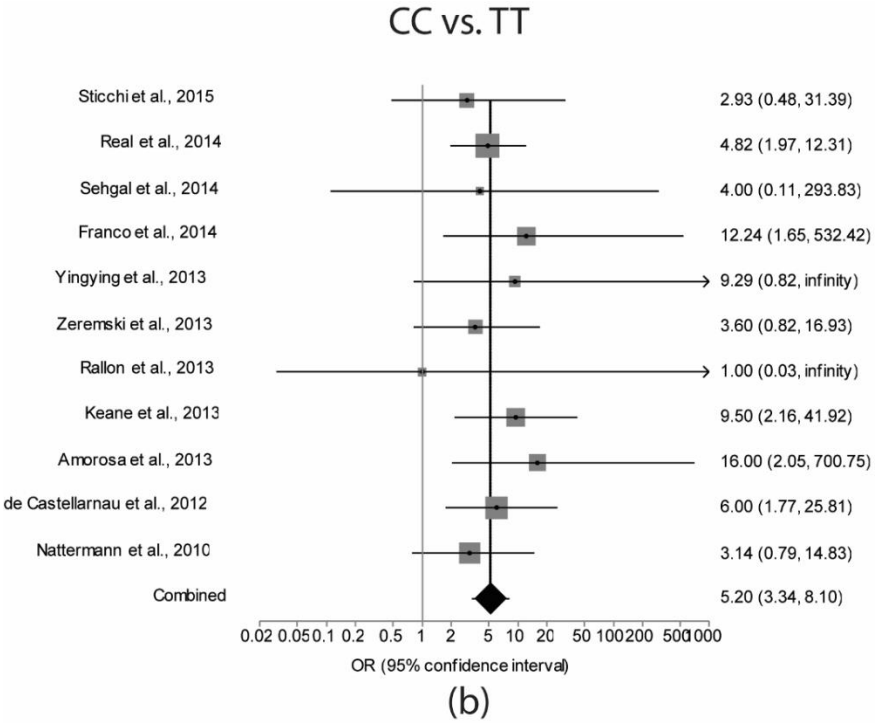
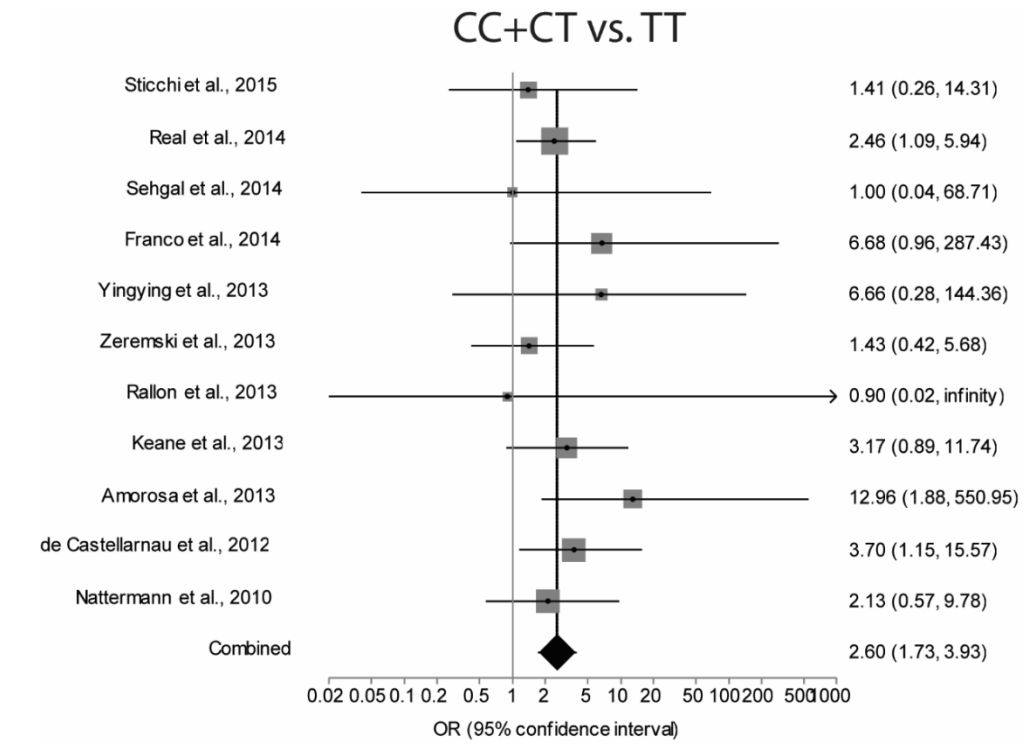
Real, 2014
Sehgal, 2014
Franco, 2014
Matas, 2014
Corchado, 2014
Torres-Cornejo, 2014
Mandorfer, 2014
Neukam, 2013
Yingying, 2013
Zeremski, 2013
Rallon, 2013
Keane, 2013
Mandorfer, 2013
Amorosa, 2013
Neukam, 2012
Osinusi, 2012
Stenkvist, 2012
Rivero-Juarez , 2012
Rallón, 2012
Mira, 2012
de Castellarnau, 2012
Vispo, 2012
Labarga, 2012
López-Cortés, 2012
Naggie, 2012
Rallón, 2011
Dayyeh, 2011
Labarga, 2011
Nattermann, 2010
Rallón, 2010
Pineda, 2010
combined [random]
2.60 (0.99, 6.95)
4.83 (2.73, 8.57)
3.98 (1.08, 15.21)
3.60 (2.09, 6.23)
8.00 (0.66, 116.13)
2.60 (1.39, 4.90)
4.92 (1.29, 19.77)
3.78 (2.19, 6.53)
0.53 (0.19, 1.53)
1.80 (0.85, 3.87)
2.34 (1.19, 4.63)
3.73 (0.63, 26.68)
3.09 (1.24, 7.73)
1.25 (0.15, 10.79)
6.48 (2.62, 17.47)
2.17 (1.41, 3.36)
2.99 (1.20, 7.36)
3.94 (2.69, 5.78)
0.80 (0.09, 6.38)
2.00 (0.07, 141.23)
1.40 (0.47, 4.10)
3.02 (1.29, 7.19)
9.00 (2.45, 34.53)
3.56 (1.88, 6.76)
4.05 (1.53, 10.91)
5.32 (2.87, 9.94)
1.14 (0.30, 4.31)
7.14 (1.35, 40.85)
5.42 (2.77, 10.69)
2.15 (0.29, 25.70)
3.85 (1.16, 13.17)
2.04 (1.10, 3.78)
4.77 (2.32, 9.93)
4.72 (2.25, 9.96)
3.20 (2.69, 3.80)
0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200
odds ratio (95% confidence interval)

(e)

Fig. 4.2 The forest plots for the association between the *IL28B* rs12979860 polymorphism on SVR in HCV 1/4 subtypes taken together in the (a) allele contrast, (b) homozygote contrast, (c) dominant, (d) additive and (e) recessive genetic models.






CC+CT vs. TT
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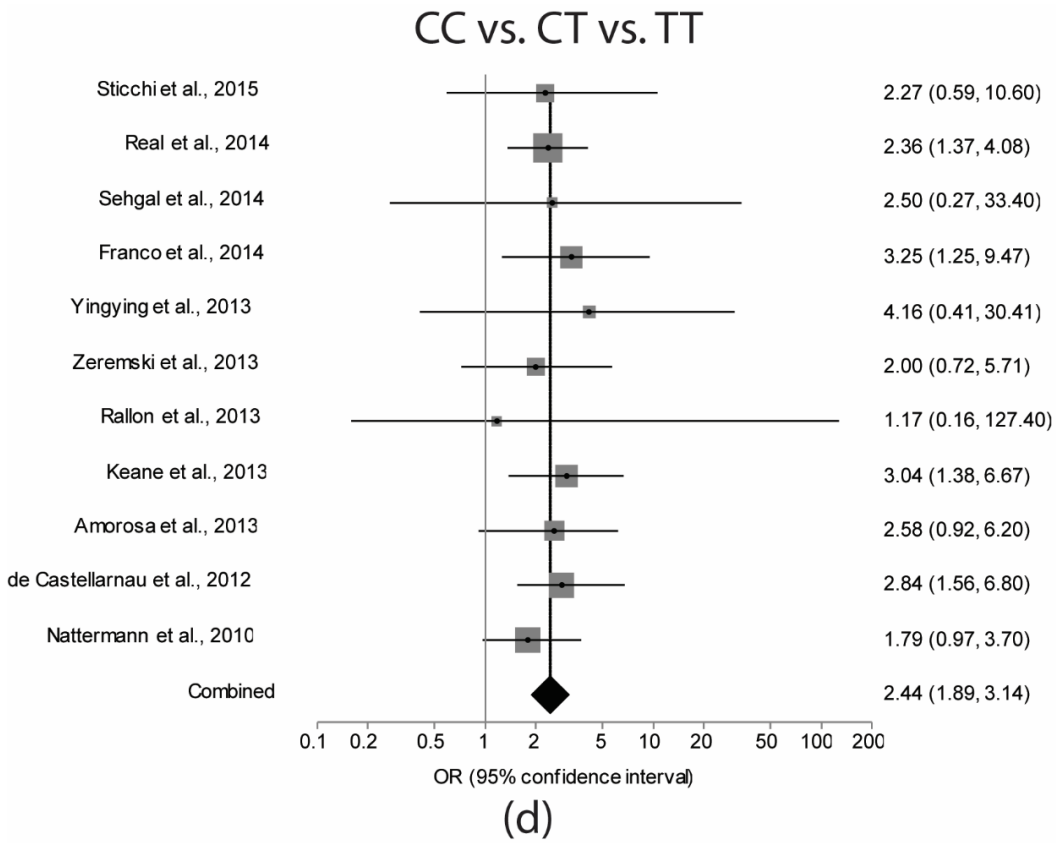
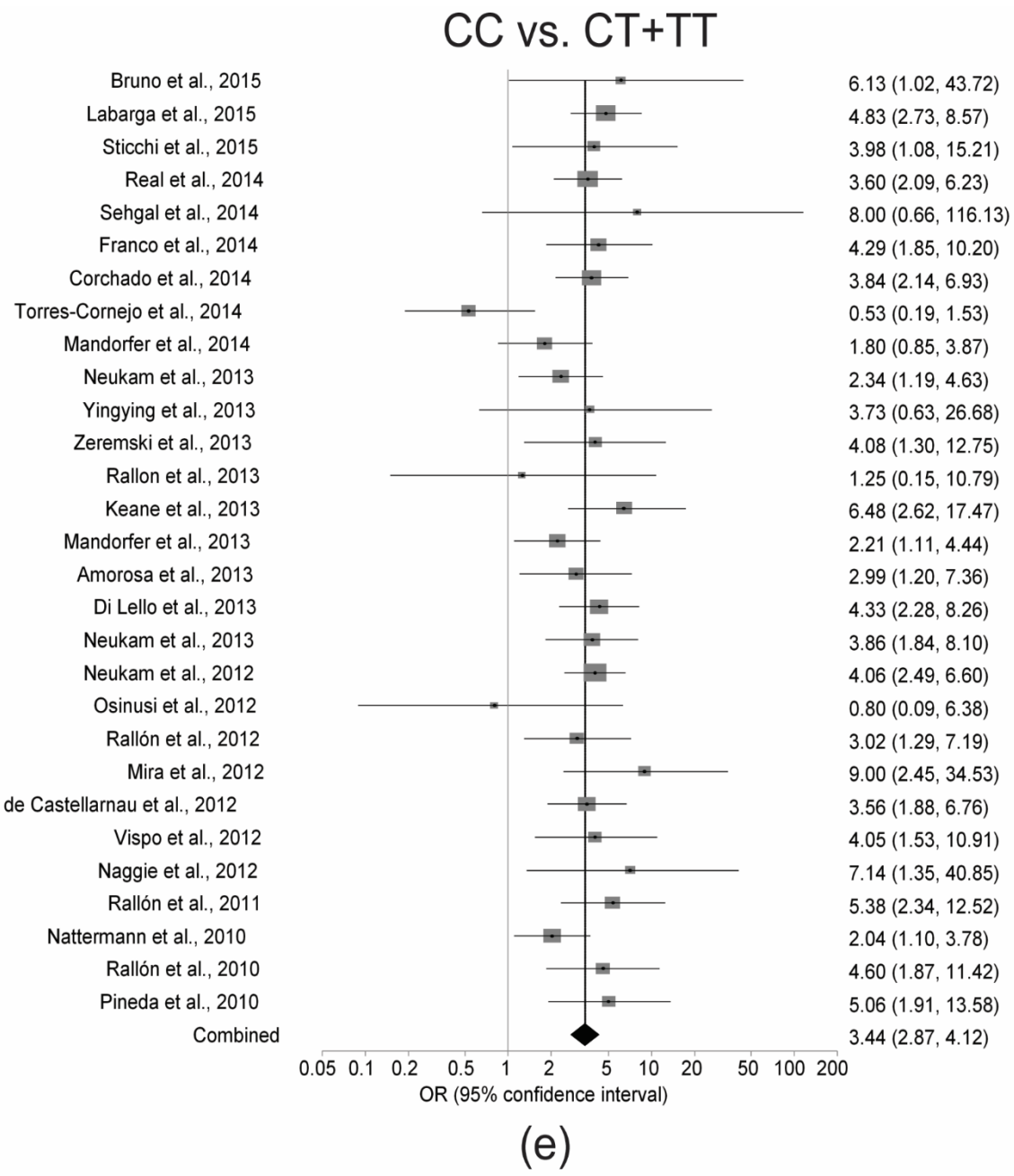
Real et al., 2014
Sehgal et al., 2014
Franco et al., 2014
Yingying et al., 2013
Zeremski et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
1.41 (0.26, 14.31)
2.46 (1.09, 5.94)
1.00 (0.04, 68.71)
6.68 (0.96, 287.43)
6.66 (0.28, 144.36)
1.43 (0.42, 5.68)
0.90 (0.02, infinity)
3.17 (0.89, 11.74)
12.96 (1.88, 550.95)
3.70 (1.15, 15.57)
2.13 (0.57, 9.78)
2.60 (1.73, 3.93)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200 500 1000
OR (95% confidence interval)

(c)


CC vs. CT vs. TT
Sticchi et al., 2015
Real et al., 2014
Sehgal et al., 2014
Franco et al., 2014
Yingying et al., 2013
Zeremski et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
2.27 (0.59, 10.60)
2.36 (1.37, 4.08)
2.50 (0.27, 33.40)
3.25 (1.25, 9.47)
4.16 (0.41, 30.41)
2.00 (0.72, 5.71)
1.17 (0.16, 127.40)
3.04 (1.38, 6.67)
2.58 (0.92, 6.20)
2.84 (1.56, 6.80)
1.79 (0.97, 3.70)
2.44 (1.89, 3.14)
0.1 0.2 0.5 1 2 5 10 20 50 100 200
OR (95% confidence interval)

(d)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Labarga et al., 2015
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Sehgal et al., 2014
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Corchado et al., 2014
Torres-Cornejo et al., 2014
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Yingying et al., 2013
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Neukam et al., 2012
Osinusi et al., 2012
Rallón et al., 2012
Mira et al., 2012
de Castellarnau et al., 2012
Vispo et al., 2012
Naggie et al., 2012
Rallón et al., 2011
Nattermann et al., 2010
Rallón et al., 2010
Pineda et al., 2010
Combined
6.13 (1.02, 43.72)
4.83 (2.73, 8.57)
3.98 (1.08, 15.21)
3.60 (2.09, 6.23)
8.00 (0.66, 116.13)
4.29 (1.85, 10.20)
3.84 (2.14, 6.93)
0.53 (0.19, 1.53)
1.80 (0.85, 3.87)
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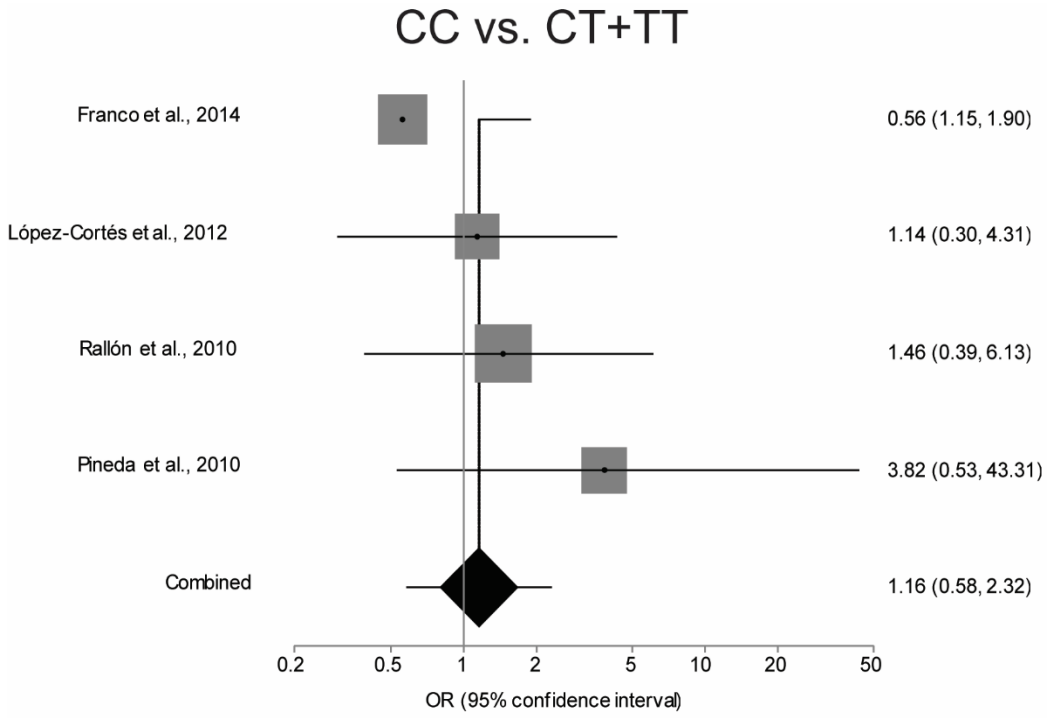
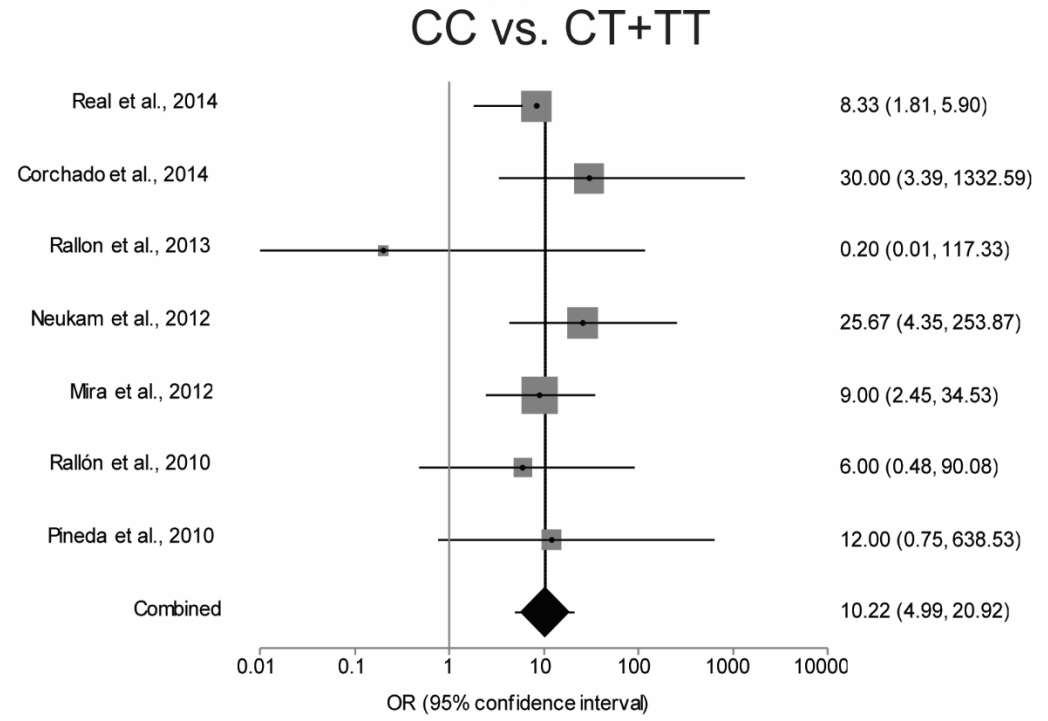
4.06 (2.49, 6.60)
0.80 (0.09, 6.38)
3.02 (1.29, 7.19)
9.00 (2.45, 34.53)
3.56 (1.88, 6.76)
4.05 (1.53, 10.91)
7.14 (1.35, 40.85)
5.38 (2.34, 12.52)
2.04 (1.10, 3.78)
4.60 (1.87, 11.42)
5.06 (1.91, 13.58)
3.44 (2.87, 4.12)
0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200
OR (95% confidence interval)

(e)

Fig. 4.3 The forest plots for the association between the *IL28B* rs12979860 polymorphism on SVR in (a) HCV 3 subtype and (b) HCV 4 subtype in the recessive model.

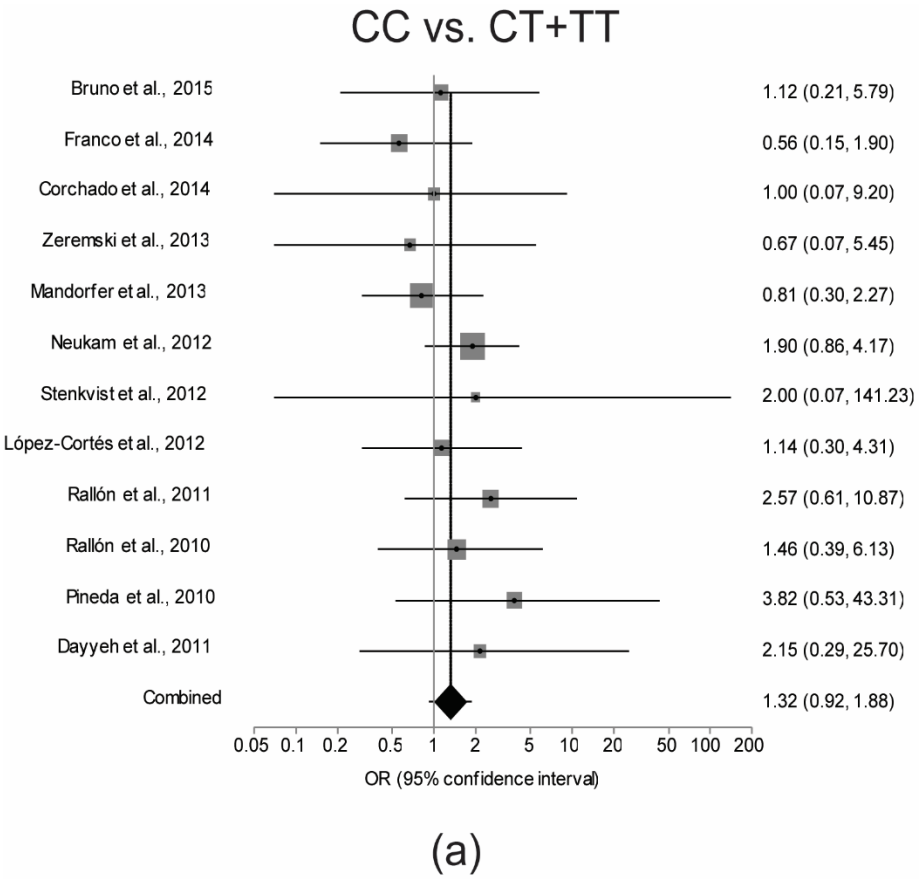


(a)



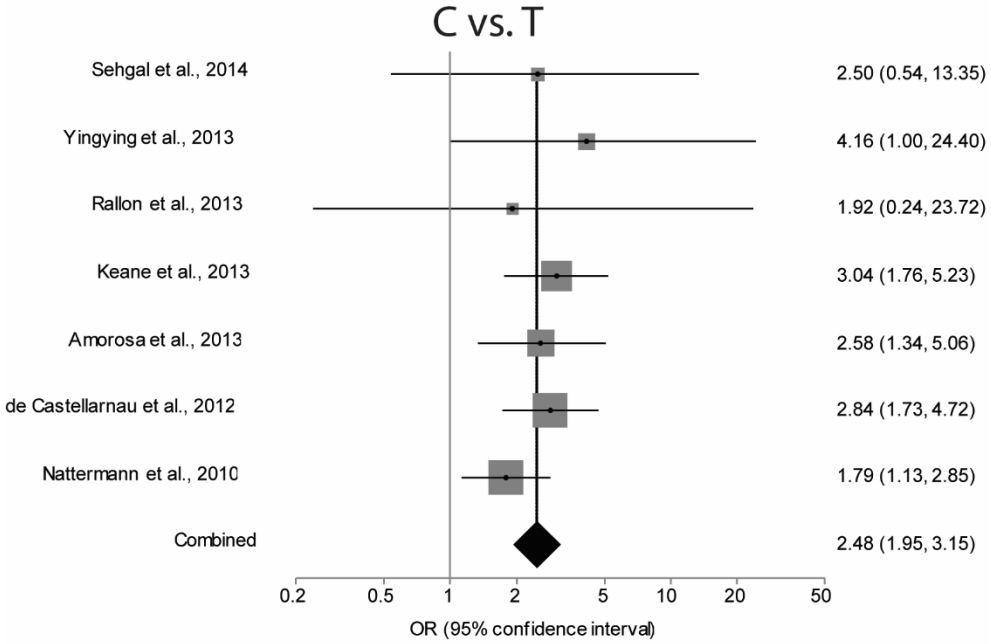
(b)

Fig. 4.4 The forest plots for the association between the *IL28B* rs12979860 polymorphism on SVR in HCV 2/3 subtypes taken together in the recessive model.

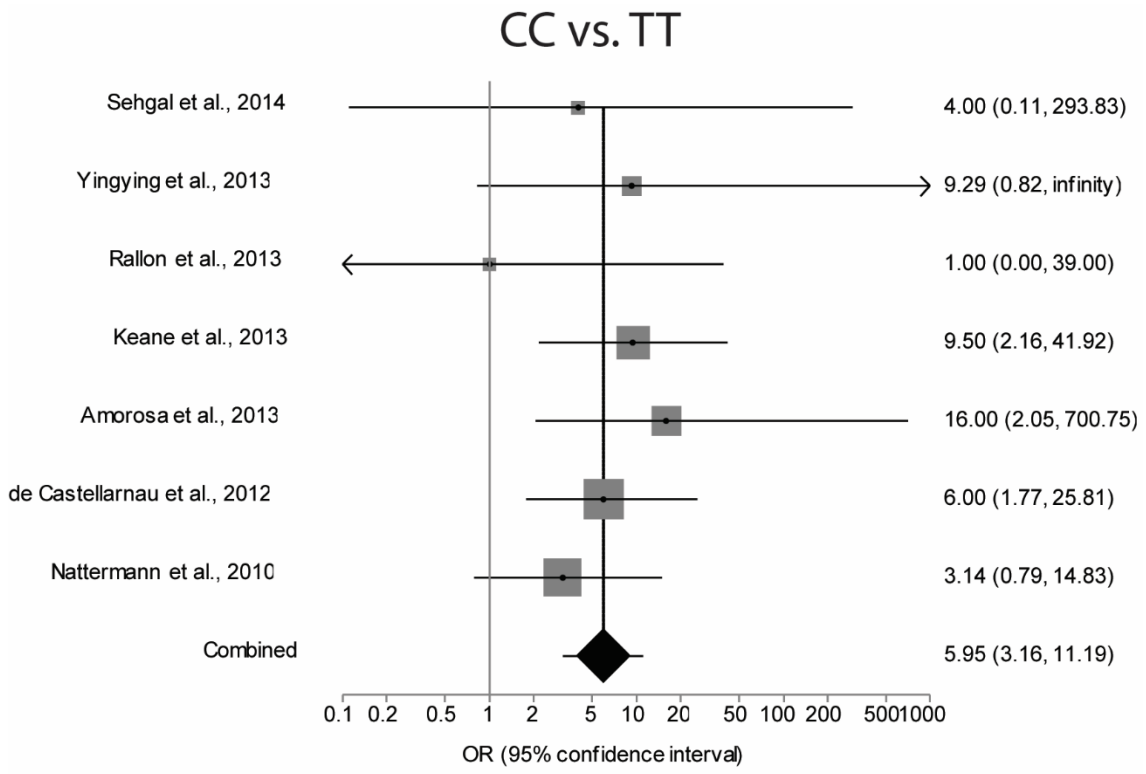


(a)

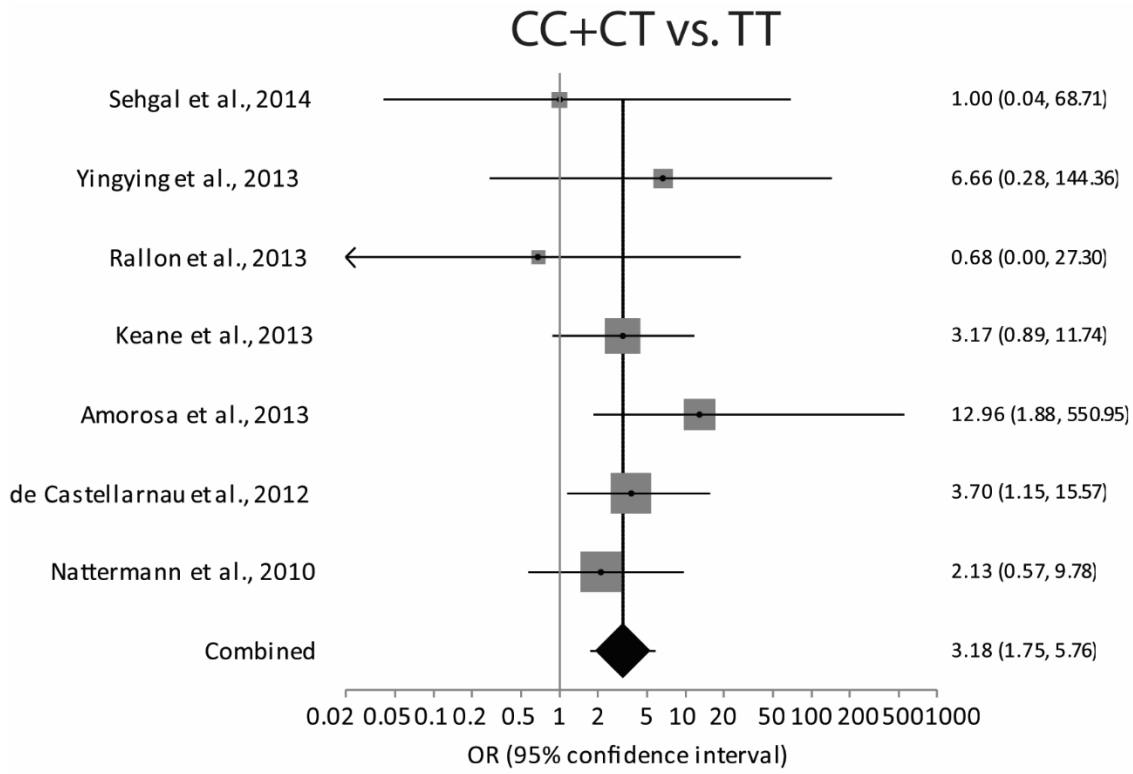
Fig. 7.5 The forest plots for the association between the *IL28B* rs12979860 polymorphism on SVR in HCV 1 subtypes taken together in the (a) allele contrast, (b) homozygote contrast, (c) dominant, (d) additive and (e) recessive genetic models.



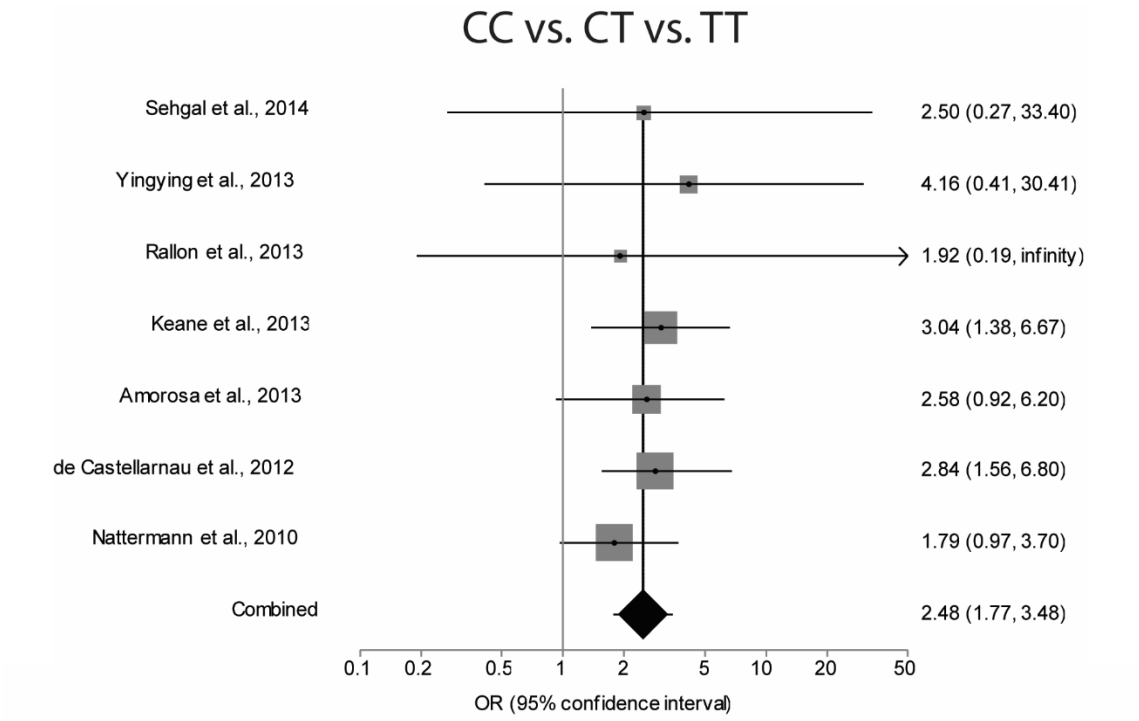
(a)


CC vs. TT
Sehgal et al., 2014
Yingying et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
4.00 (0.11, 293.83)
9.29 (0.82, infinity)
1.00 (0.00, 39.00)
9.50 (2.16, 41.92)
16.00 (2.05, 700.75)
6.00 (1.77, 25.81)
3.14 (0.79, 14.83)
5.95 (3.16, 11.19)
0.1 0.2 0.5 1 2 5 10 20 50 100 200 5001000
OR (95% confidence interval)

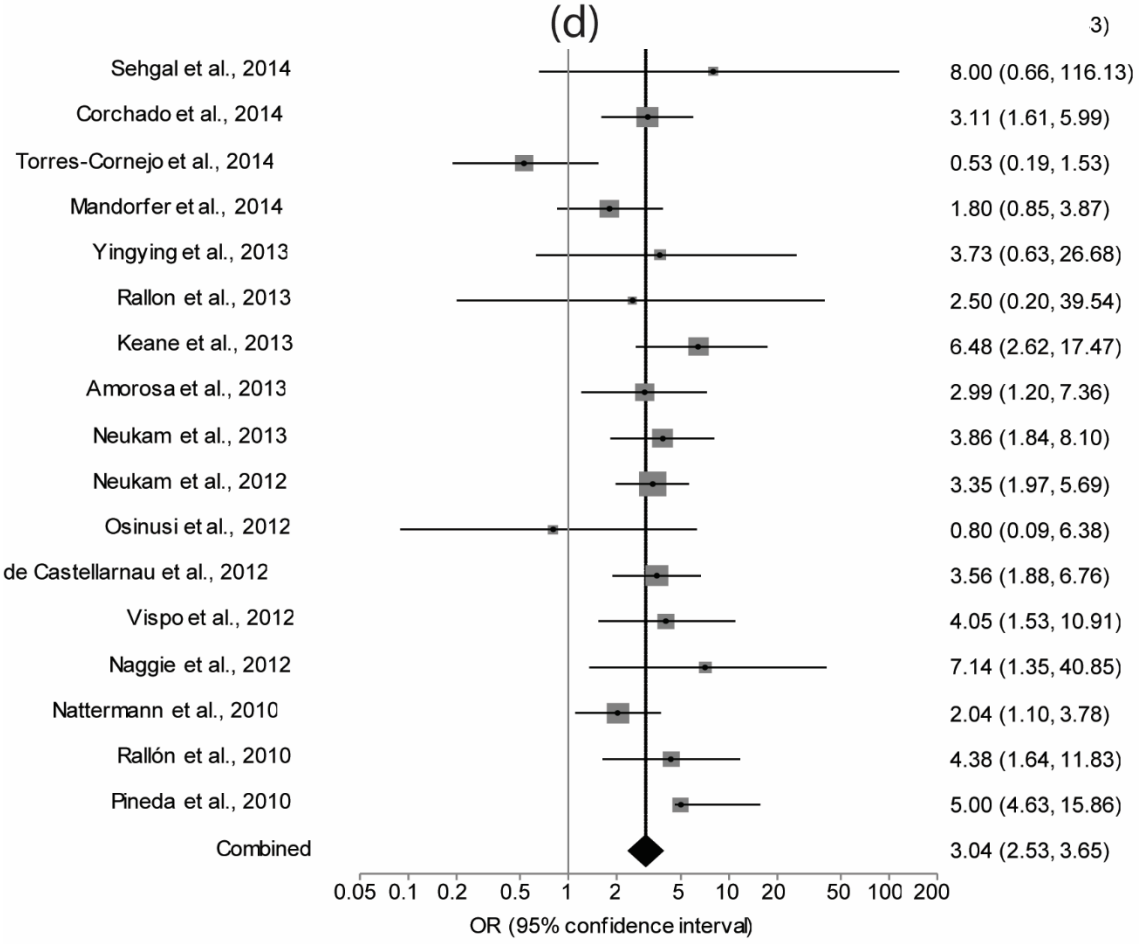
(b)


CC+CT vs. TT
Sehgal et al., 2014
Yingying et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
1.00 (0.04, 68.71)
6.66 (0.28, 144.36)
0.68 (0.00, 27.30)
3.17 (0.89, 11.74)
12.96 (1.88, 550.95)
3.70 (1.15, 15.57)
2.13 (0.57, 9.78)
3.18 (1.75, 5.76)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200 5001000
OR (95% confidence interval)

(c)

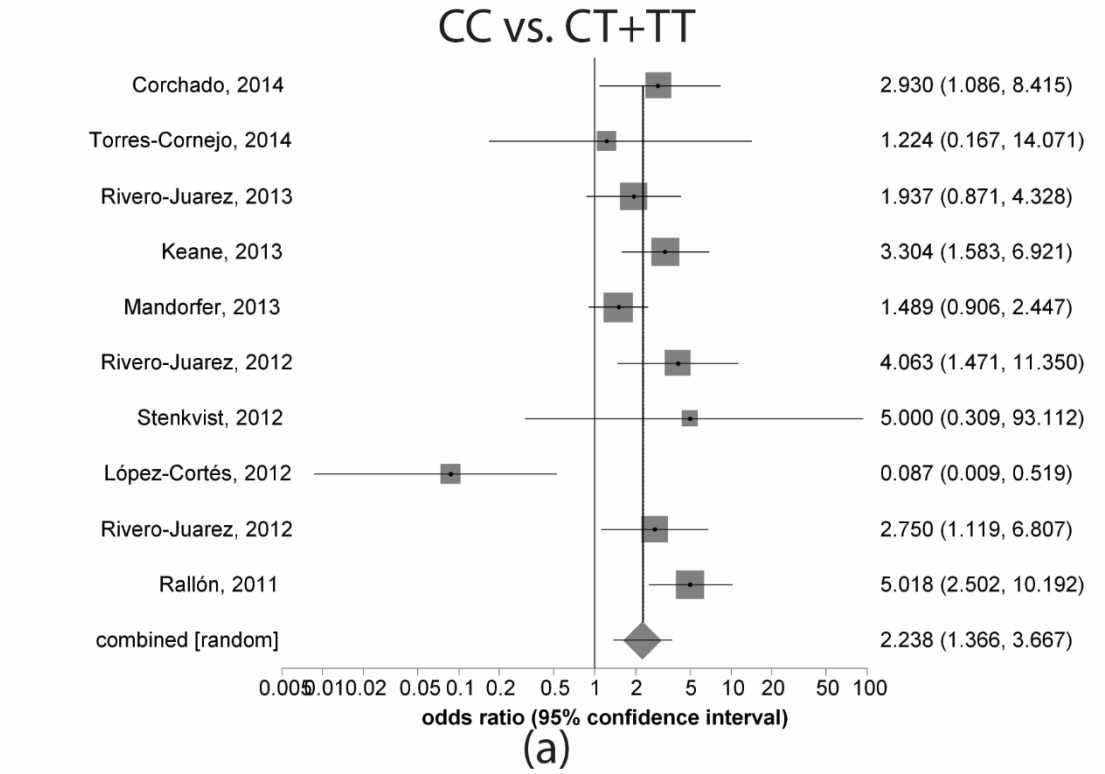

CC vs. CT vs. TT
Sehgal et al., 2014
Yingying et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
de Castellarnau et al., 2012
Nattermann et al., 2010
Combined
2.50 (0.27, 33.40)
4.16 (0.41, 30.41)
1.92 (0.19, infinity)
3.04 (1.38, 6.67)
2.58 (0.92, 6.20)
2.84 (1.56, 6.80)
1.79 (0.97, 3.70)
2.48 (1.77, 3.48)
0.1 0.2 0.5 1 2 5 10 20 50
OR (95% confidence interval)

(d)

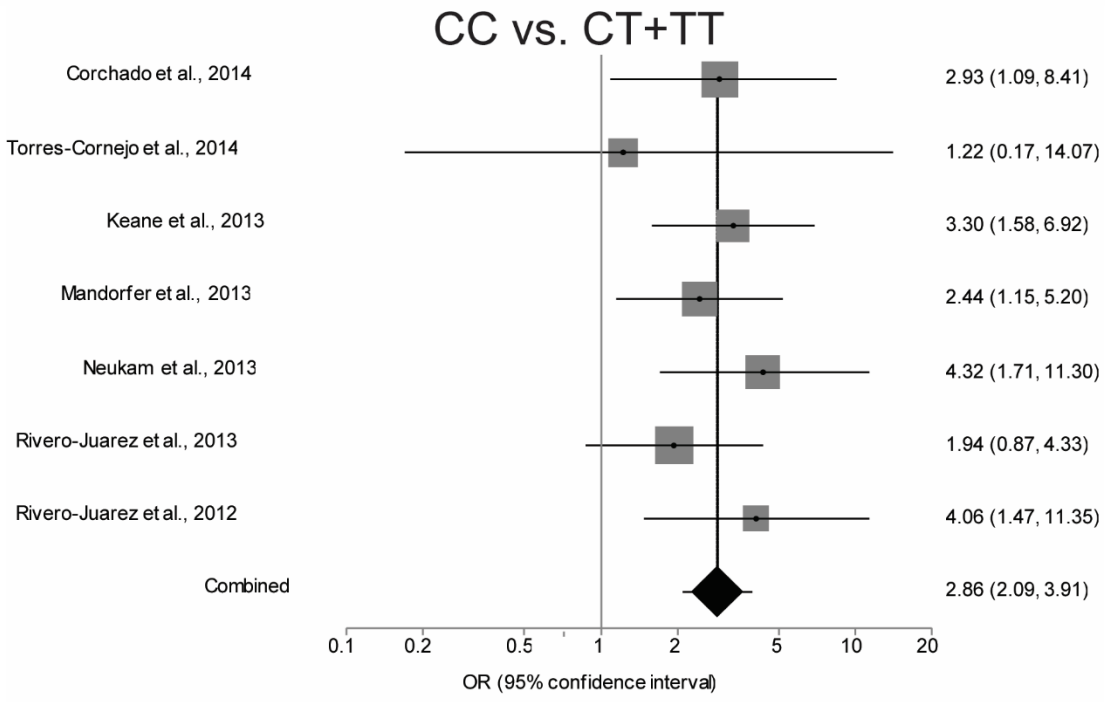

3)
Sehgal et al., 2014
Corchado et al., 2014
Torres-Cornejo et al., 2014
Mandorfer et al., 2014
Yingying et al., 2013
Rallon et al., 2013
Keane et al., 2013
Amorosa et al., 2013
Neukam et al., 2013
Neukam et al., 2012
Osinusi et al., 2012
de Castellarnau et al., 2012
Vispo et al., 2012
Naggie et al., 2012
Nattermann et al., 2010
Rallón et al., 2010
Pineda et al., 2010
Combined
8.00 (0.66, 116.13)
3.11 (1.61, 5.99)
0.53 (0.19, 1.53)
1.80 (0.85, 3.87)
3.73 (0.63, 26.68)
2.50 (0.20, 39.54)
6.48 (2.62, 17.47)
2.99 (1.20, 7.36)
3.86 (1.84, 8.10)
3.35 (1.97, 5.69)
0.80 (0.09, 6.38)
3.56 (1.88, 6.76)
4.05 (1.53, 10.91)
7.14 (1.35, 40.85)
2.04 (1.10, 3.78)
4.38 (1.64, 11.83)
5.00 (4.63, 15.86)
3.04 (2.53, 3.65)
0.05 0.1 0.2 0.5 1 2 5 10 20 50 100 200
OR (95% confidence interval)

(e)

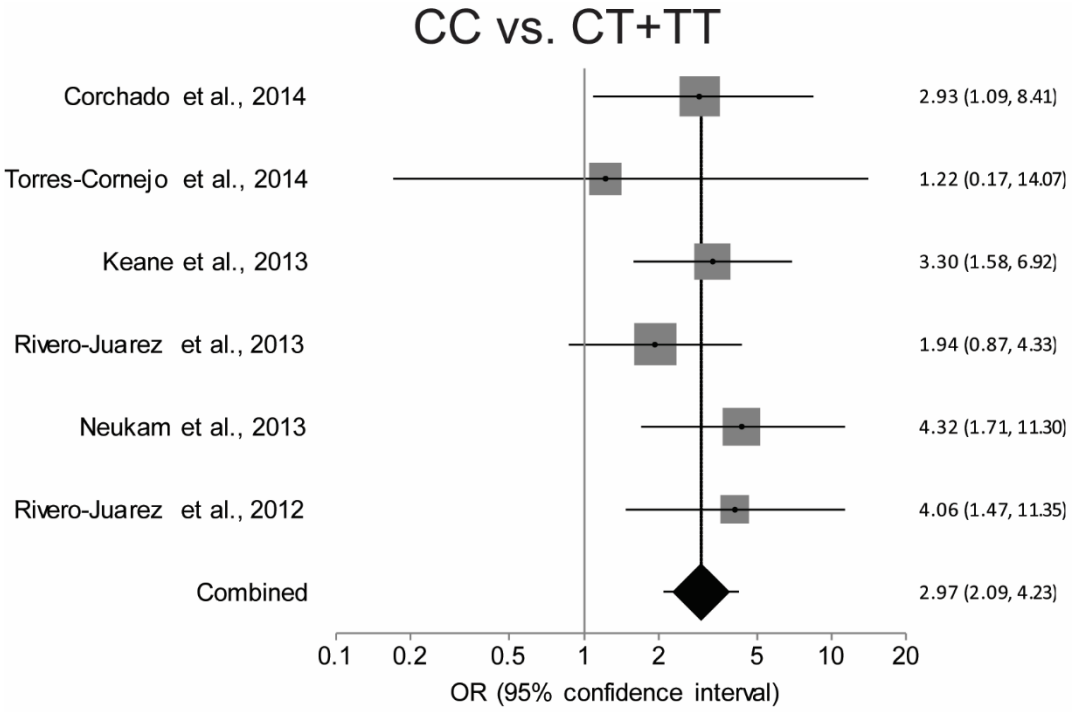
Fig. 4.6 The forest plots for the association between the *IL28B* rs12979860 polymorphism on RVR in (a) all HCV subtypes, (b) HCV 1/4, (c) HCV 1, and (d) HCV 2/3 subtypes in the recessive model.



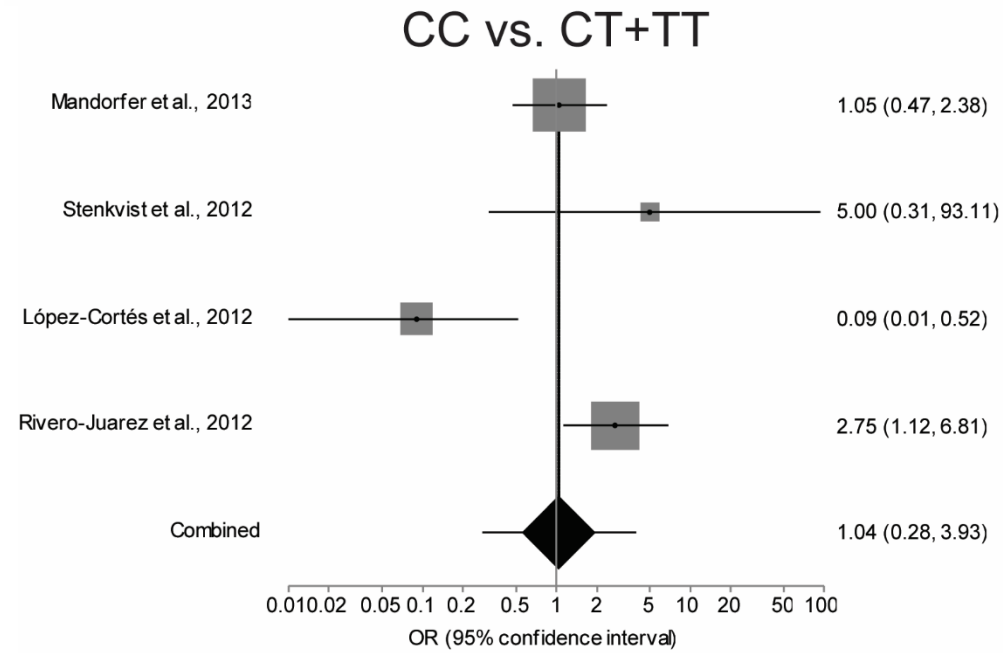
(a)



(b)

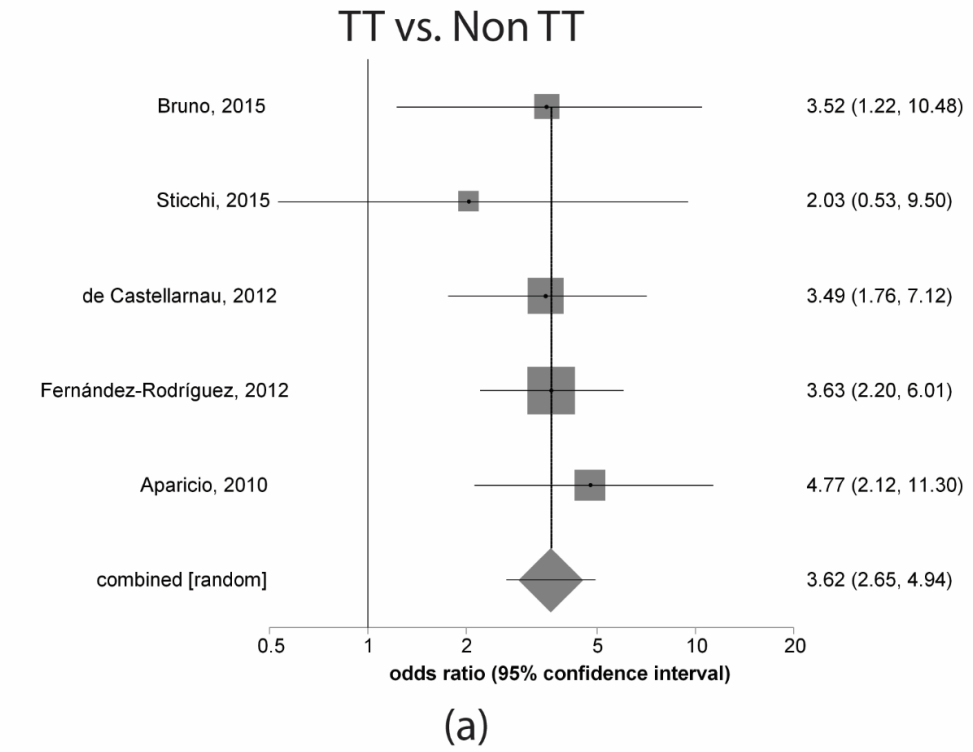

CC vs. CT+TT
Corchado et al., 2014
Torres-Cornejo et al., 2014
Keane et al., 2013
Rivero-Juarez et al., 2013
Neukam et al., 2013
Rivero-Juarez et al., 2012
Combined
2.93 (1.09, 8.41)
1.22 (0.17, 14.07)
3.30 (1.58, 6.92)
1.94 (0.87, 4.33)
4.32 (1.71, 11.30)
4.06 (1.47, 11.35)
2.97 (2.09, 4.23)
0.1 0.2 0.5 1 2 5 10 20
OR (95% confidence interval)

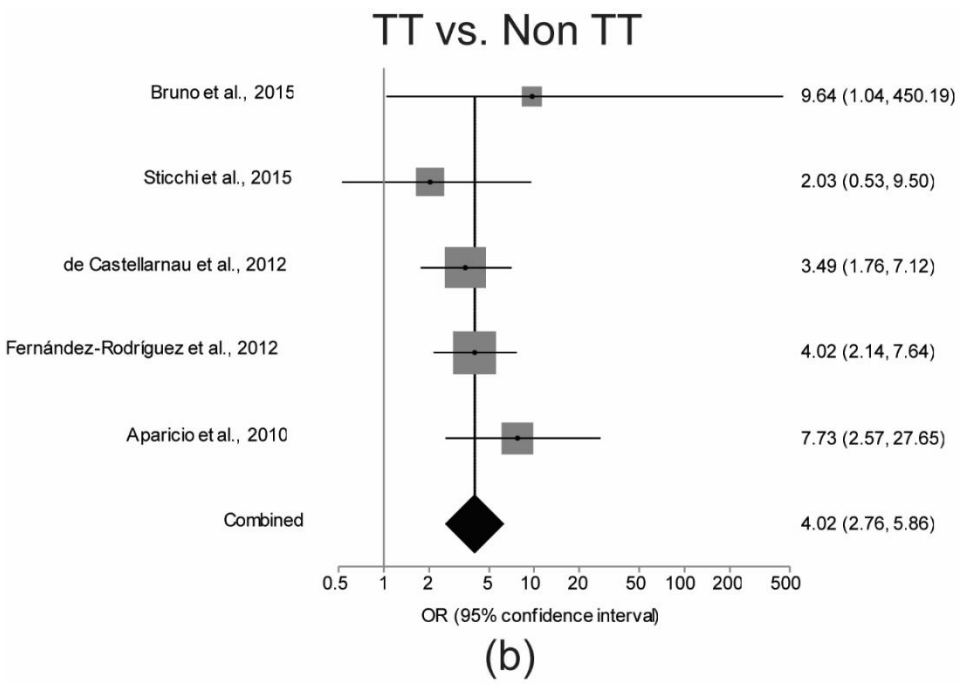
(c)


CC vs. CT+TT
Mandorfer et al., 2013
Stenkvist et al., 2012
López-Cortés et al., 2012
Rivero-Juarez et al., 2012
Combined
1.05 (0.47, 2.38)
5.00 (0.31, 93.11)
0.09 (0.01, 0.52)
2.75 (1.12, 6.81)
1.04 (0.28, 3.93)
0.010.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100
OR (95% confidence interval)

(d)

Fig4.7 The forest plots for the association between the *IL28B* rs8099917 polymorphism on SVR in (a) all HCV subtypes, (b) HCV 1/4, and (c) HCV 2/3 subtypes in the recessive model.





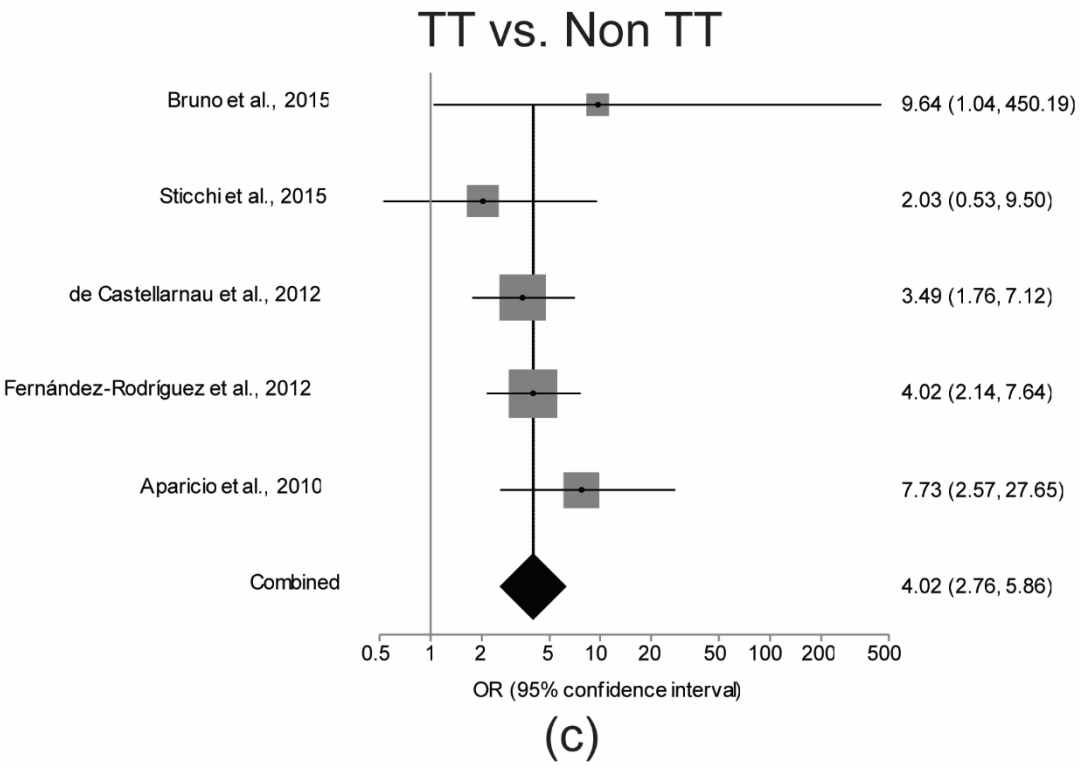


Fig. 4.8 The forest plots for the association between the IL28B rs12980275 polymorphism on SVR in (a) all HCV subtypes taken together in the recessive model.

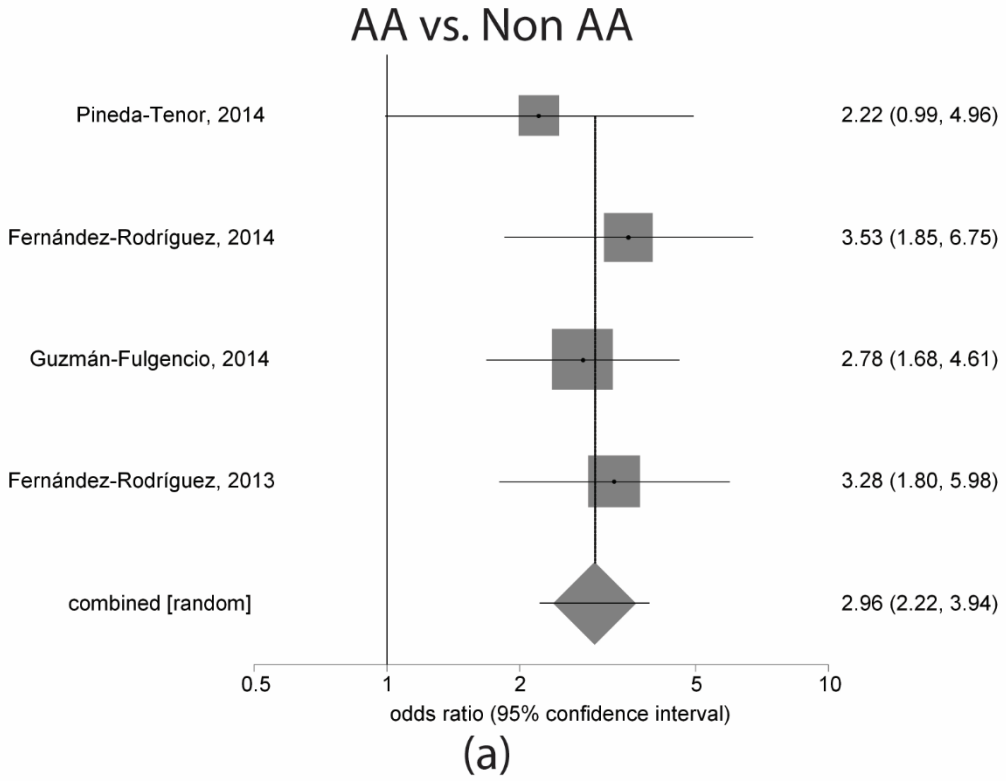
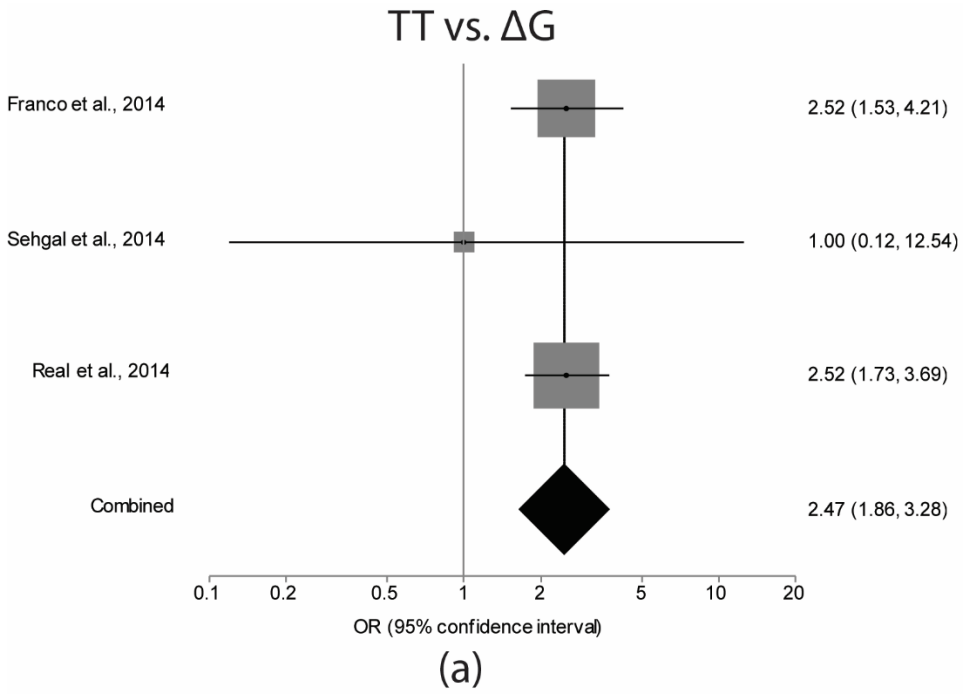
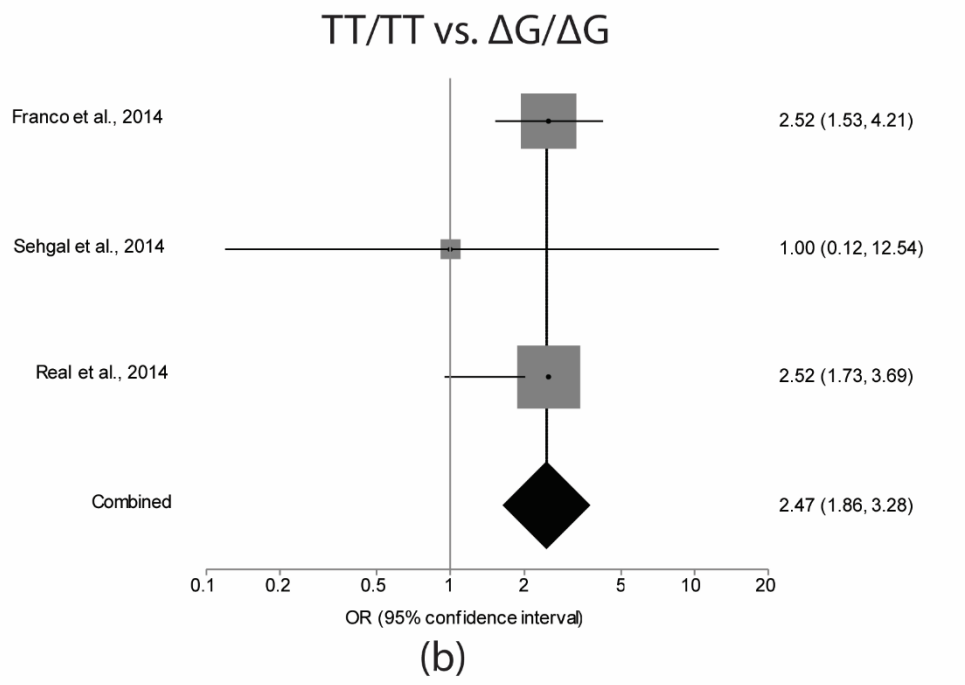
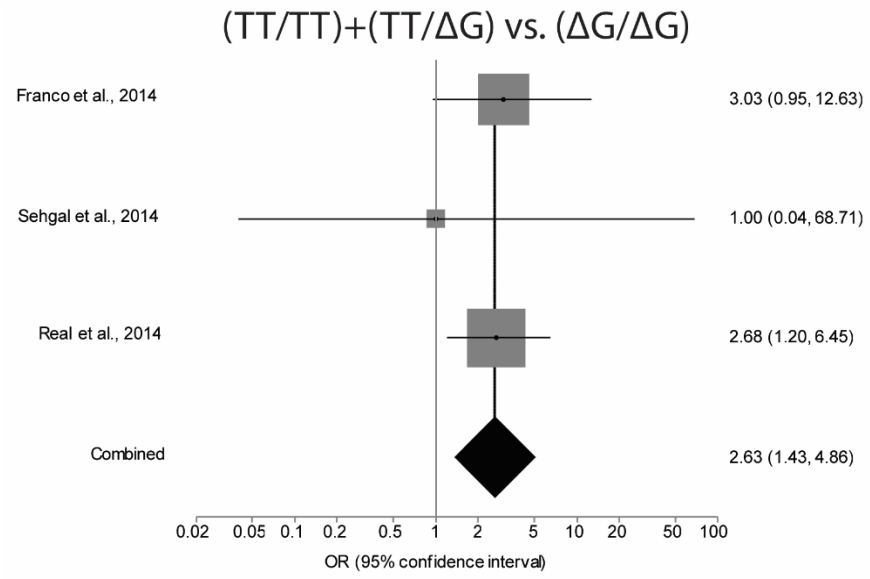


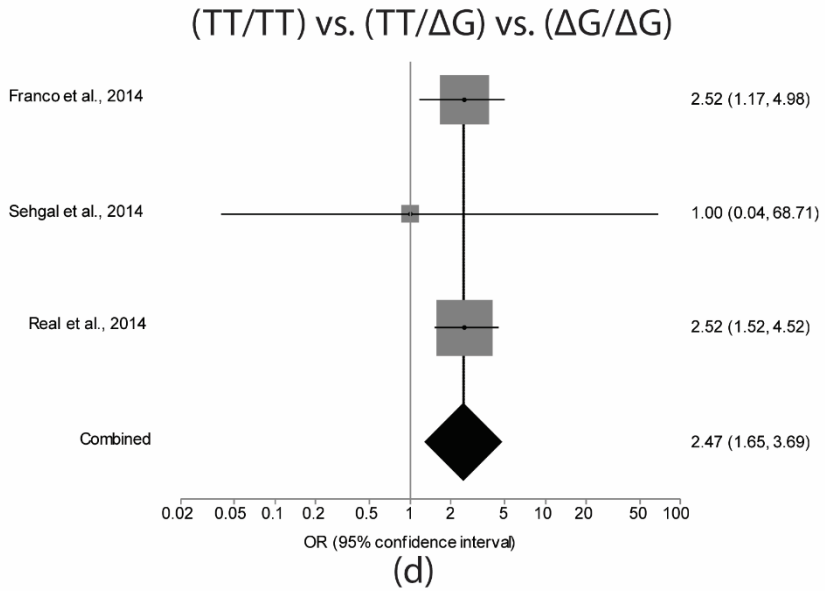
Fig. 4.9 The forest plots for the association between the *IL28B* dinucleotide variant ss469415590 on SVR in all HCV subtypes taken together in the (a) allele contrast, (b) homozygote contrast, (c) dominant, (d) additive and (e) recessive genetic models.



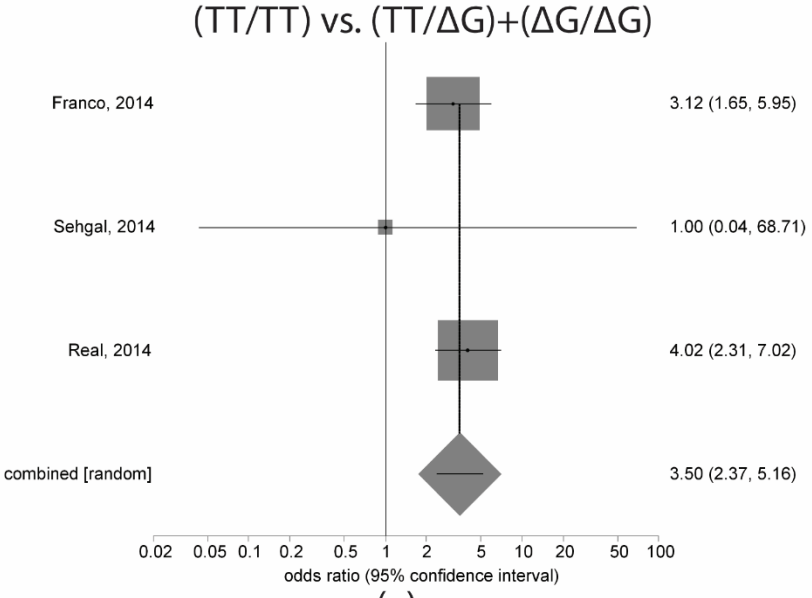



(TT/TT)+(TT/ΔG) vs. (ΔG/ΔG)
Franco et al., 2014
3.03 (0.95, 12.63)
Sehgal et al., 2014
1.00 (0.04, 68.71)
Real et al., 2014
2.68 (1.20, 6.45)
Combined
2.63 (1.43, 4.86)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100
OR (95% confidence interval)

(c)


(TT/TT) vs. (TT/ΔG) vs. (ΔG/ΔG)
Franco et al., 2014
2.52 (1.17, 4.98)
Sehgal et al., 2014
1.00 (0.04, 68.71)
Real et al., 2014
2.52 (1.52, 4.52)
Combined
2.47 (1.65, 3.69)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100
OR (95% confidence interval)

(d)


(TT/TT) vs. (TT/ΔG)+(ΔG/ΔG)
Franco, 2014
3.12 (1.65, 5.95)
Sehgal, 2014
1.00 (0.04, 68.71)
Real, 2014
4.02 (2.31, 7.02)
combined [random]
3.50 (2.37, 5.16)
0.02 0.05 0.1 0.2 0.5 1 2 5 10 20 50 100
odds ratio (95% confidence interval)

(e)

Fig. 5 Flow chart illustrating the study selection in Chapter 2

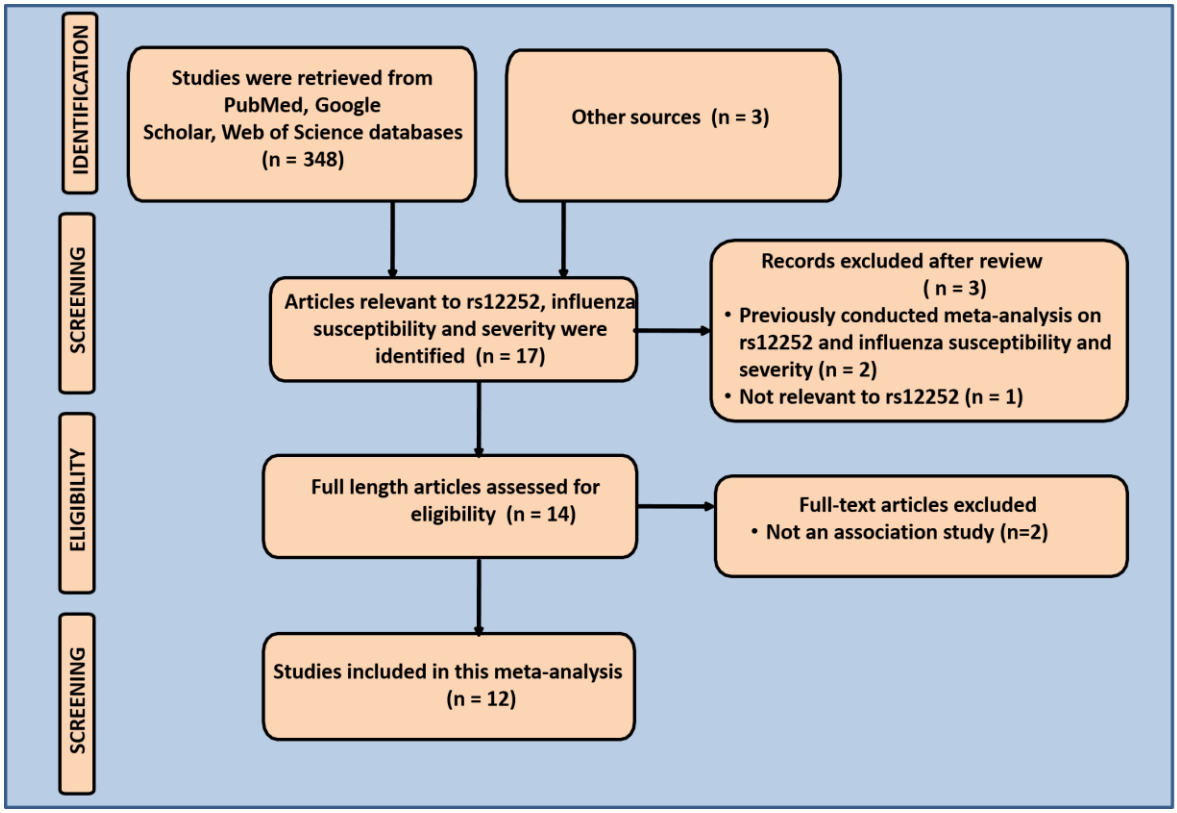
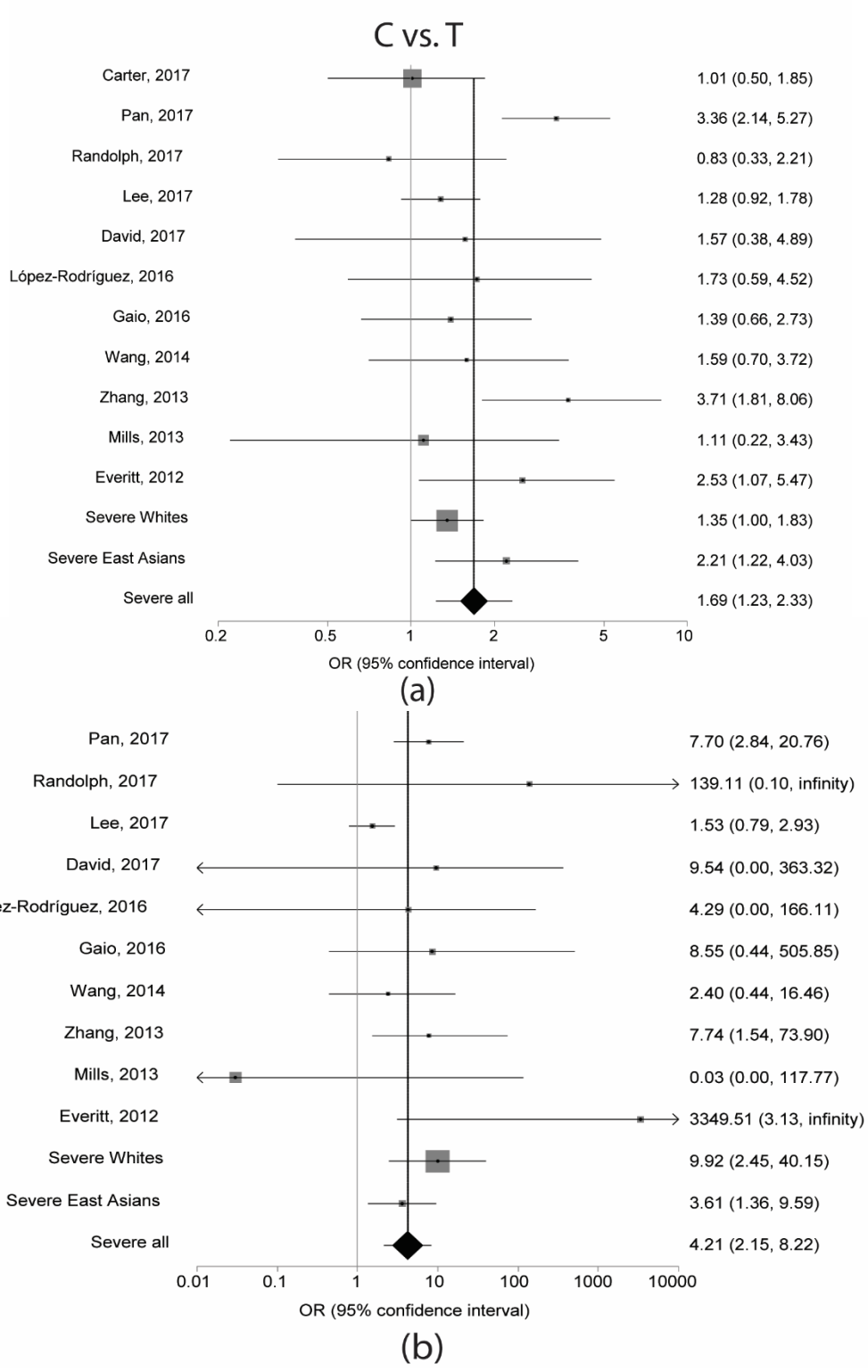
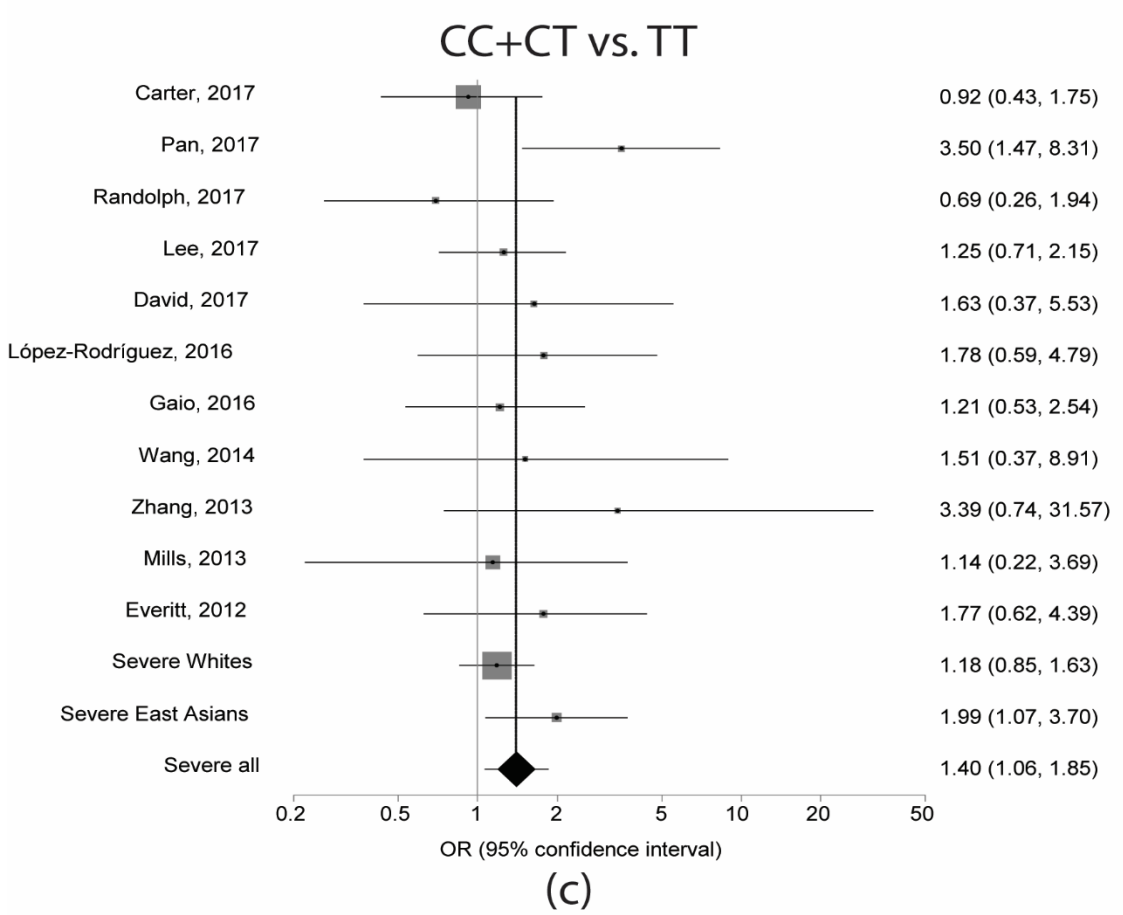
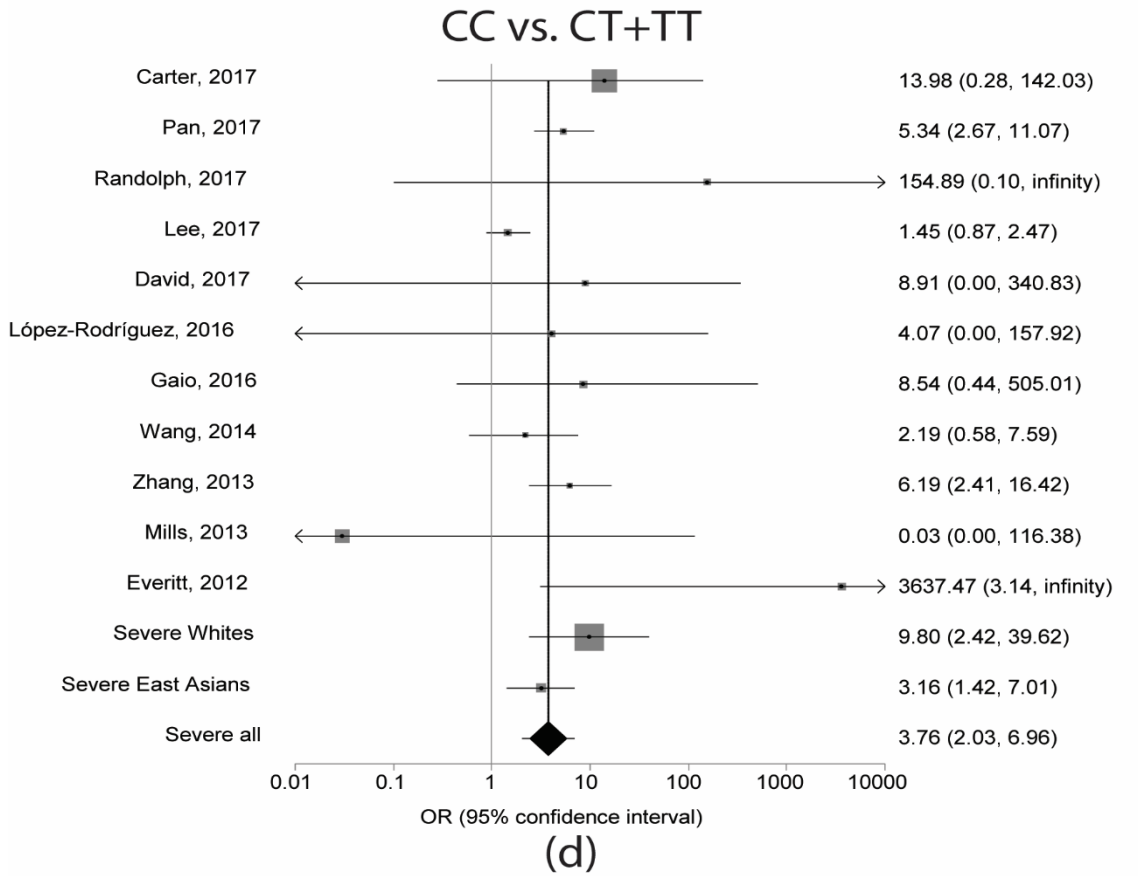


Fig. 6.1 The forest plots for the association between the *IFITM3* rs12252 polymorphism and influenza susceptibility to severe influenza in the (a) allele contrast, (b) homozygote contrast, (c) dominant and (d) recessive genetic models.



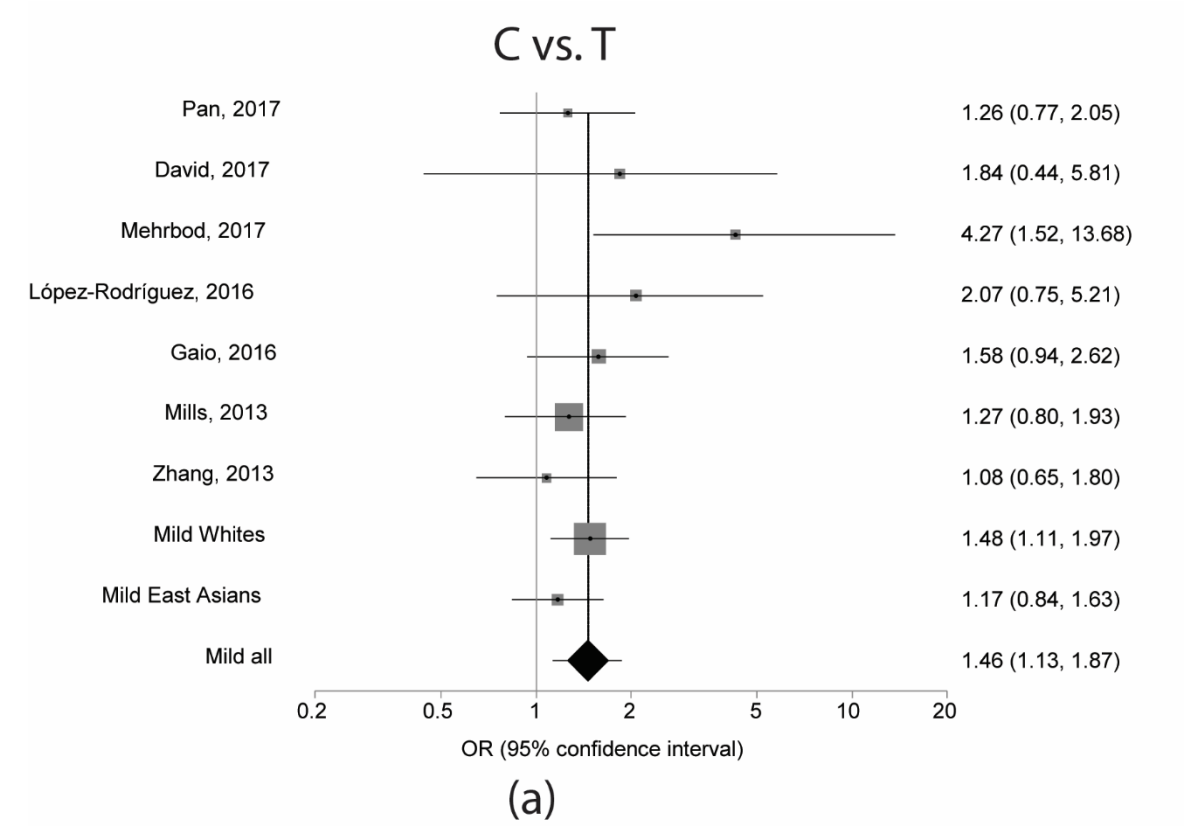

CC+CT vs. TT
Carter, 2017
Pan, 2017
Randolph, 2017
Lee, 2017
David, 2017
López-Rodríguez, 2016
Gaio, 2016
Wang, 2014
Zhang, 2013
Mills, 2013
Everitt, 2012
Severe Whites
Severe East Asians
Severe all
0.92 (0.43, 1.75)
3.50 (1.47, 8.31)
0.69 (0.26, 1.94)
1.25 (0.71, 2.15)
1.63 (0.37, 5.53)
1.78 (0.59, 4.79)
1.21 (0.53, 2.54)
1.51 (0.37, 8.91)
3.39 (0.74, 31.57)
1.14 (0.22, 3.69)
1.77 (0.62, 4.39)
1.18 (0.85, 1.63)
1.99 (1.07, 3.70)
1.40 (1.06, 1.85)
0.2
0.5
1
2
5
10
20
50
OR (95% confidence interval)

(c)

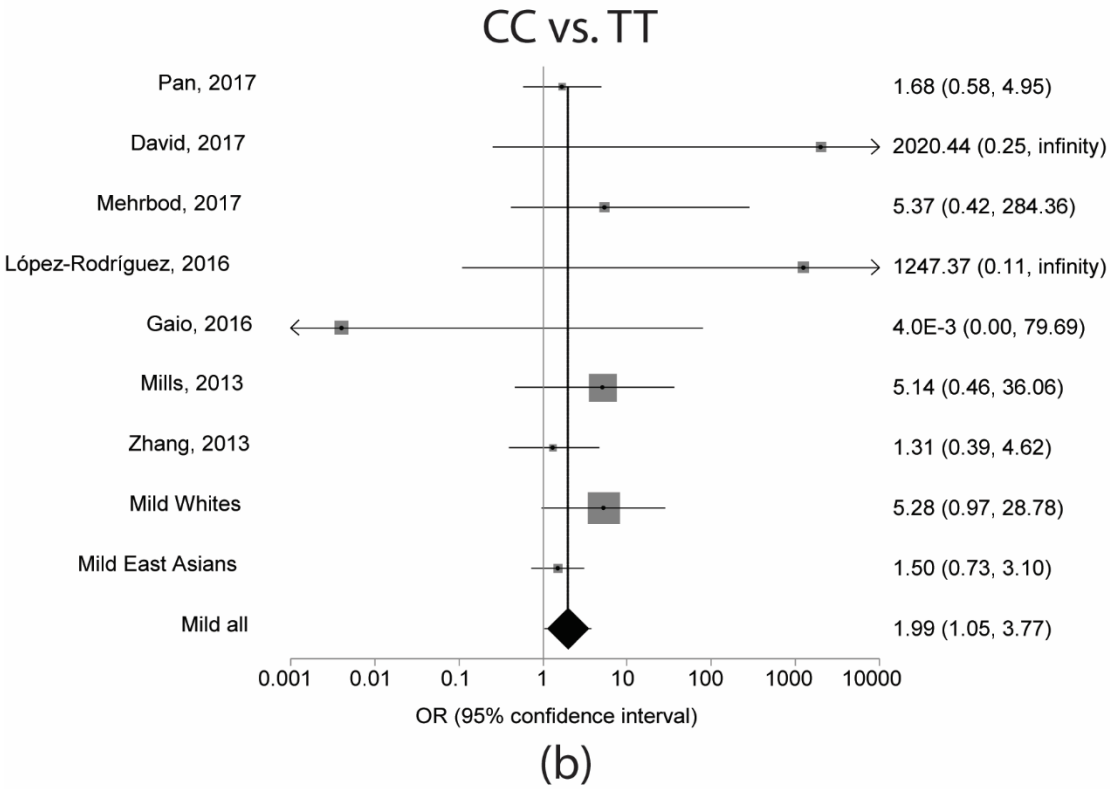

CC vs. CT+TT
Carter, 2017
Pan, 2017
Randolph, 2017
Lee, 2017
David, 2017
López-Rodríguez, 2016
Gaio, 2016
Wang, 2014
Zhang, 2013
Mills, 2013
Everitt, 2012
Severe Whites
Severe East Asians
Severe all
13.98 (0.28, 142.03)
5.34 (2.67, 11.07)
154.89 (0.10, infinity)
1.45 (0.87, 2.47)
8.91 (0.00, 340.83)
4.07 (0.00, 157.92)
8.54 (0.44, 505.01)
2.19 (0.58, 7.59)
6.19 (2.41, 16.42)
0.03 (0.00, 116.38)
3637.47 (3.14, infinity)
9.80 (2.42, 39.62)
3.16 (1.42, 7.01)
3.76 (2.03, 6.96)
0.01
0.1
1
10
100
1000
10000
OR (95% confidence interval)

(d)

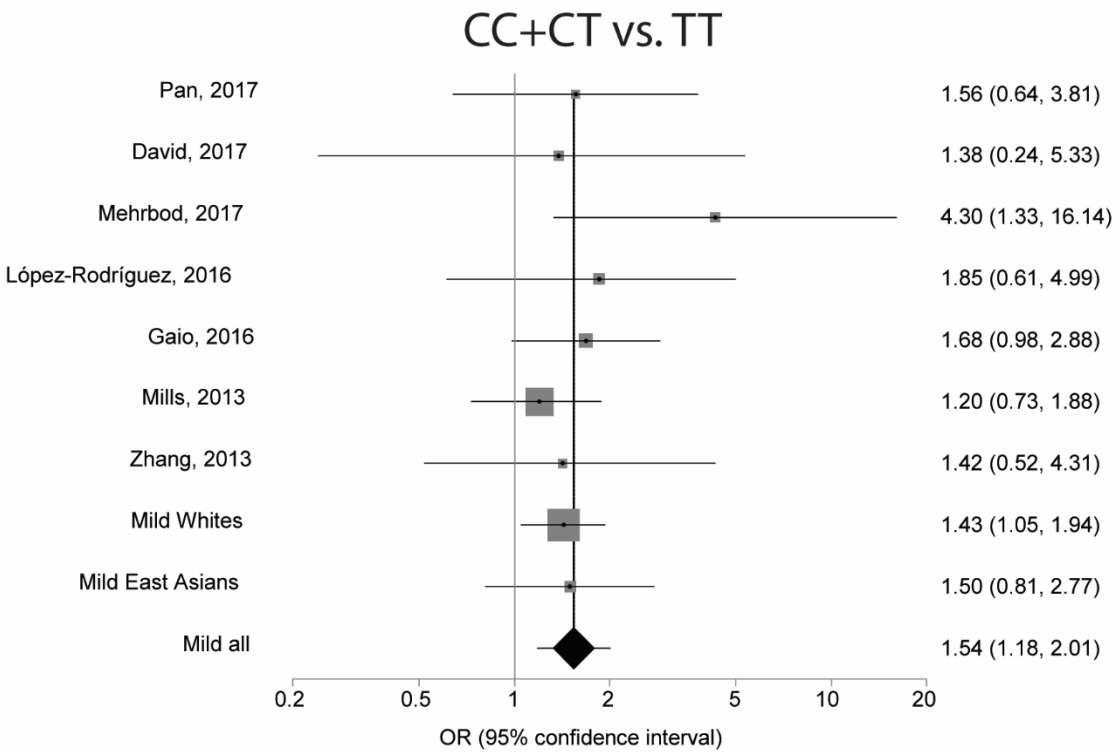
Fig. 6.2 The forest plots for the association between the *IFITM3* rs12252 polymorphism and influenza susceptibility to mild influenza in the (a) allele contrast, (b) homozygote contrast, (c) dominant and (d) recessive genetic models.



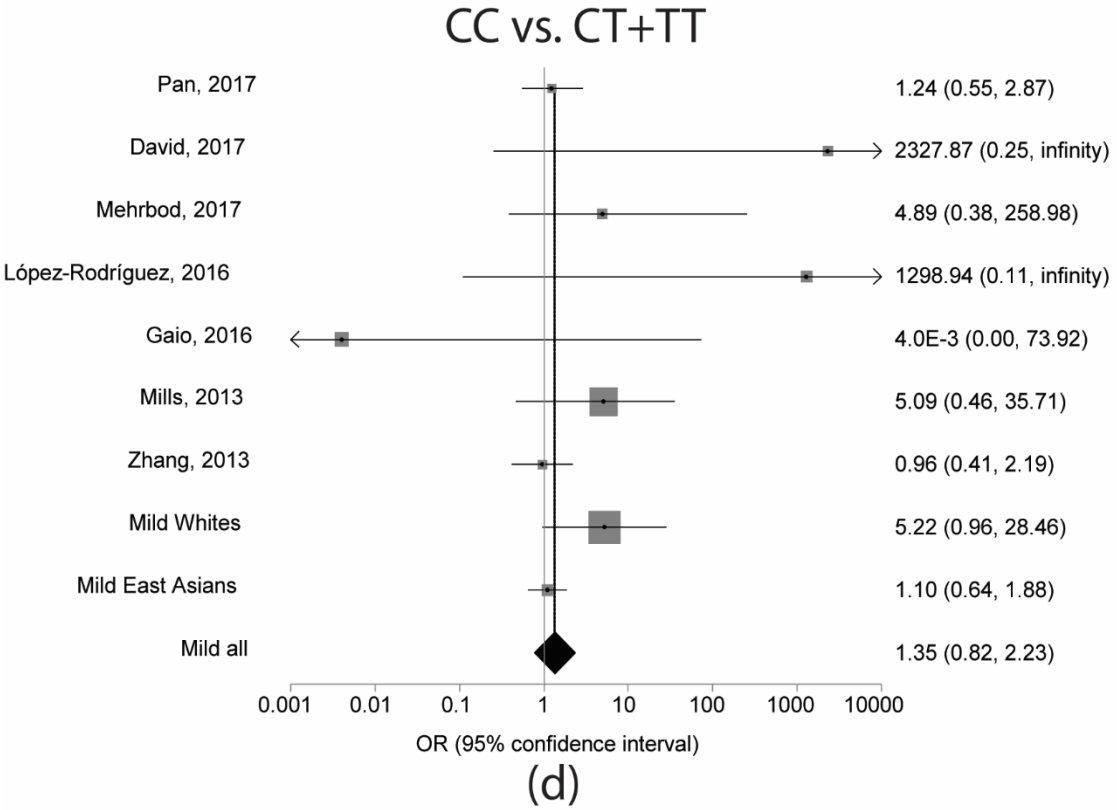
(a)



(b)


CC+CT vs. TT
Pan, 2017
David, 2017
Mehrbod, 2017
López-Rodríguez, 2016
Gaio, 2016
Mills, 2013
Zhang, 2013
Mild Whites
Mild East Asians
Mild all
1.56 (0.64, 3.81)
1.38 (0.24, 5.33)
4.30 (1.33, 16.14)
1.85 (0.61, 4.99)
1.68 (0.98, 2.88)
1.20 (0.73, 1.88)
1.42 (0.52, 4.31)
1.43 (1.05, 1.94)
1.50 (0.81, 2.77)
1.54 (1.18, 2.01)
0.2
0.5
1
2
5
10
20
OR (95% confidence interval)

(c)


CC vs. CT+TT
Pan, 2017
David, 2017
Mehrbod, 2017
López-Rodríguez, 2016
Gaio, 2016
Mills, 2013
Zhang, 2013
Mild Whites
Mild East Asians
Mild all
1.24 (0.55, 2.87)
2327.87 (0.25, infinity)
4.89 (0.38, 258.98)
1298.94 (0.11, infinity)
4.0E-3 (0.00, 73.92)
5.09 (0.46, 35.71)
0.96 (0.41, 2.19)
5.22 (0.96, 28.46)
1.10 (0.64, 1.88)
1.35 (0.82, 2.23)
0.001
0.01
0.1
1
10
100
1000
10000
OR (95% confidence interval)

(d)

List of Tables

Table 1 Reported SNPs near IL28B gene

S. No.	Polymorphism	Type of polymorphism	Location	Alleles
1	rs4803217	SNV	3’ UTR Variant	C>A
2	rs11881222	SNV	Intron variant	A>G
3	rs8103142	SNV	CDS variant	T>C
4	rs28416813	SNV	Intron variant	C>G
5	rs4803219	SNV	5’ UTR Variant	C>T
6	rs8113007	SNV	Intron variant	A>T
7	rs12980275	SNV	NA	A>G
8	ss469415590	FSV	NA	TT/G
9	rs12979860	SNV	Intron variant	C>T

Table 2 Characteristics of the study involving IL28B gene

No.	REFERENCE	PLACE OF STUDY	GENDER (M/F) : MEDIAN AGE (RANGE)	DETECTION METHOD	HCV sub-types	Type of virological response	SNPs present	SVR / Non SVR	RVR / Non RVR
1	Lui et al., 2015	Taiwan	106/10 : 36.5 (27-46)	Taqman assay	1/2/3/6	SVR	rs8099917	86/32	
2	Bruno et al., 2015	Italy	89/13 : 41 (24-50)	qPCR	1/2/3/4	SVR	rs12979860, rs8099917	46/39	-
3	Labarga et al., 2015	Spain	253/86 : 41.4 (36.2-46.6)	Not Mentioned	1/4	SVR	rs12979860	101/158	-
4	Sticchi et al., 2015	Italy	20/68 : 49.7 (38.2-61.02)	qPCR	1/4	SVR	rs12979860, rs8099917	15/73	-
5	Real et al., 2014	Spain	216/56 : 43 (38.7-46.7)	qPCR	1/4	SVR	rs12979860, ss469415590	122/150	-
6	Sehgal et al., 2014	United States	20/1 : 46.5 (43-48)	Taqman assay	1	SVR	rs12979860, ss469415590	7/14	-
7	Franco et al., 2014	Spain	148/98 : 42.3 (40.54-44.49)	Taqman assay	1/3/4	SVR	rs12979860, ss469415590	73/134	-
8	Matas et al., 2014	Spain	N M : 41.53 (36.1-46.96)	RFLP, DNA seq	1/3/4	SVR,RVR	rs12979860	24/31	6/51

9	Corchado et al., 2014	Spain	222/45 : 41.5 (36-47)	qPCR, Line probe assay	1/2/3/4	SVR,RVR	rs12979860	113/154	23/164
10	Torres-Cornejo et al., 2014	Spain	98/22 : 41 (32-58)	Taqman assay	1	SVR,RVR	rs12979860	92/22	108/6
11	Mandorfer et al., 2014	Austria, Spain, Italy, Germany, Poland	119/29 : 40.2 (32.4-48)	Not Mentioned	1	SVR	rs12979860	77/59	-
12	Neukam et al., 2013	Spain	170/35 : 41.6 (38.5-44.8)	Golden gate assay	1/4	SVR	rs12979860	73/89	-
13	Yingying et al., 2013	China	18/18 : N M	Taqman assay	1	SVR	rs12979860	10/26	-
14	Zeremski et al., 2013	United States	81/34 : 46.7(39.2-54.2)	Taqman assay	1/2/3/4	SVR	rs12979860	34/79	-
15	Rallon et al., 2013	Spain	13/6 : 40.9 (38-55)	Taqman assay	1/4	SVR	rs12979860	9/10	-
16	Keane et al., 2013	Austria, Ireland	108/35 : 44.7(43.13-46.76)	Taqman assay	1	SVR,RVR	rs12979860	101/48	61/88
17	Mandorfer et al., 2013	Austria, Spain, Italy, Germany, Poland	348/82 : 41.5 (34.2-48.8)	Not Mentioned	1/2/3/4	SVR,RVR	rs12979860	228/202	129/170
18	Amorosa et al., 2013	United States	151/32 : 48 (41-52)	iPlex Sequenom assay	1	SVR	rs12979860	34/96	-

19	Di Lello et al., 2013	Spain	251/63 : 41.5 (38.5-44.8)	qPCR	1/4	SVR	rs12979860	77/136	-
20	Neukam et al., 2013	Spain	134/26 : 41 (39-45)	Taqman assay	1	SVR,RVR	rs12979860	58/102	29/131
21	Neukam et al., 2012	Spain, Germany	420/101 : 42 (39-46)	LightSNiP-Typing assay	1/2/3/4	SVR	rs12979860	240/279	-
22	Osinusi et al., 2012	United States	20/2 : 42.3 (38-51)	Taqman assay	1	SVR	rs12979860	9/13	-
23	Stenkvist et al., 2012	Sweden	11/2 : 50.5 (38-62)	Taqman assay	2/3	SVR,RVR	rs12979860	10/3	6/7
24	Rivero-Juarez et al., 2012	Spain	106/24 : 40.9 (35.5-46.3)	Taqman assay	1/4/3	SVR	rs12979860	84/21	-
25	Rallón et al., 2012	Spain	84/28 : 42 (39-46)	Taqman assay	1/4	SVR	rs12979860	63/49	-
26	Mira et al., 2012	Spain	486/91 : 41.5 (37-46)	Taqman assay	4	SVR	rs12979860	24/60	-
27	de Castellarnau et al., 2012	Spain	134/63 : 47.8 (46.4-49.1)	Direct PCR amplification and sequencing	1	SVR	rs12979860, rs8099917	83/114	-
28	Vispo et al., 2012	Spain	73/23 : 41 (38-46)	Taqman assay	1	SVR	rs12979860	40/56	-
29	Labarga et al., 2012	Spain	261/96 : 43 (37.5-48.5)	Taqman assay	1/2/3/4	SVR	rs12979860	118/110	-
30	López-Cortés et al., 2012	Spain	48/10 : 44 (27-57)	Taqman assay	3	SVR,RVR	rs12979860	30/18	29/16
31	Naggie et al., 2012	United States	39/5 : 48 (42-52)	Taqman assay	1	SVR	rs12979860	12/32	-

32	Rallón et al., 2011	Spain	147/49 : 42(38-45)	Taqman assay	1/4, 2/3	SVR,RVR	rs12979860	105/91	63/133
33	Dayyeh et al., 2011	United States	192/39 : 47(40.1-53.9)	iPlex Sequenom assay	2/3	SVR	rs12979860	21/9	-
34	Labarga et al., 2011	Spain	51/11 : 43 (Not mentioned)	Taqman assay	1/2/3/4	SVR	rs12979860	24/38	-
35	Nattermann et al., 2010	Spain, Germany	222/32 : 45.2 (28-73)	LightSNiP-Typing Assay	1	SVR	rs12979860	94/98	-
36	Rallón et al., 2010	Spain	122/42 : 42 (39-45)	Taqman assay	1/3/4	SVR	rs12979860	90/74	-
37	Pineda et al., 2010	Spain	130/24 : 42 (38-44)	Taqman assay	1/2/3/4	SVR	rs12979860	77/77	-
38	Aparicio et al., 2010	Spain	107/53 : 47.82 (46.58-49.11)	Direct PCR amplification and sequencing	1/3/4	SVR	rs8099917	67/93	-
39	Rivero-Juarez et al., 2013	Spain	177/29 : 42.1 (36.5-47.7)	Taqman assay	1	RVR	rs12979860	-	35/171
40	Rivero-Juarez et al., 2012	Spain	62/25 : 41.6 (36.9-46.9)	Taqman assay	1	RVR	rs12979860	-	36/51
41	Rivero-Juarez et al., 2012	Spain	90/16 : 42 (31.5-48.9)	Taqman assay	3	RVR	rs12979860	-	46/60
42	Pineda-Tenor et al., 2014	Spain	195/66 : 40.9 (34-47.8)	Golden gate assay	1/4	SVR	rs12980275	51/72	-
43	Fernández-Rodríguez et al., 2014	Spain	218/67 : 41.5 (38.6-45.1)	Golden gate assay	1/4	SVR	rs12980275	79/118	-

44	Guzmán-Fulgencio et al., 2014	Spain	231/73 : 42 (25-60)	Golden gate assay	1/2/3/4	SVR	rs12980275	160/114	-
45	Fernández-Rodríguez et al., 2013	Spain	249/75 : 41.9 (28.6-45.2)	Golden gate assay	1/3/4	SVR	rs8099917, rs12980275	177/147, 93/129	-

Table 3 Genotypic frequencies for all HCV subtypes

rs12979860		SVR		Non SVR	
		CC (%)	Non CC (%)	CC (%)	Non CC (%)
1	Bruno et al., 2015	26 (56.52)	20 (43.48)	13 (33.33)	26 (66.67)
2	Labarga et al., 2015	65 (64.36)	36 (35.64)	43 (27.22)	115 (72.78)
3	Sticchi et al., 2015	9 (60.00)	6 (40.00)	20 (27.40)	53 (72.60)
4	Real et al., 2014	66 (54.10)	56 (45.90)	37 (24.67)	113 (75.33)
5	Sehgal et al., 2014	4 (57.14)	3 (42.86)	2 (14.29)	12 (85.71)
6	Franco et al., 2014	46 (63.01)	27 (36.99)	53 (39.55)	81 (60.45)
7	Matas et al., 2014	13 (54.17)	11 (45.83)	6 (19.35)	25 (80.65)
8	Corchado et al., 2014	68 (60.18)	45 (39.82)	44 (28.57)	110 (71.43)
9	Torres-Cornejo et al., 2014	32 (34.78)	60 (65.22)	11 (50.00)	11 (50.00)
10	Mandorfer et al., 2014	37 (48.05)	40 (51.95)	20 (33.90)	39 (66.10)
11	Neukam et al., 2013	44 (60.27)	29 (39.73)	35 (39.33)	54 (60.67)
12	Yingying et al., 2013	7 (70.00)	3 (30.00)	10 (38.46)	16 (61.54)
13	Zeremski et al., 2013	20 (58.82)	14 (41.18)	25 (31.65)	54 (68.35)
14	Rallon et al., 2013	5 (55.56)	4 (44.44)	5 (50.00)	5 (50.00)
15	Keane et al., 2013	57 (56.44)	44 (43.56)	8 (16.67)	40 (83.33)
16	Mandorfer et al., 2013	95 (41.67)	133 (58.33)	50 (24.75)	152 (75.25)
17	Amorosa et al., 2013	16 (47.06)	18 (52.94)	22 (22.92)	74 (77.08)
18	Di Lello et al., 2013	44 (57.14)	33 (42.86)	32 (23.53)	104 (76.47)
19	Neukam et al., 2013	33 (56.89)	25 (43.10)	26 (25.49)	76 (74.51)
20	Neukam et al., 2012	151 (62.92)	89 (37.08)	84 (30.11)	195 (69.89)
21	Osinusi et al., 2012	3 (33.33)	6 (66.67)	5 (38.46)	8 (61.54)
22	Stenkvist et al., 2012	5 (50.00)	5 (50.00)	1 (33.33)	2 (66.67)
23	Rivero-Juarez et al., 2012	51 (60.71)	33 (39.29)	11 (52.38)	10 (47.62)
24	Rallón et al., 2012	36 (57.14)	27 (42.86)	15 (30.61)	34 (69.39)
25	Mira et al., 2012	12 (50.00)	12 (50.00)	6 (10.00)	54 (90.00)
26	de Castellarnau et al., 2012	56 (67.47)	27 (32.53)	42 (36.84)	72 (63.16)

27	Vispo et al., 2012	21 (52.50)	19 (47.50)	12 (21.43)	44 (78.57)
28	Labarga et al., 2012	72 (61.02)	46 (38.98)	25 (22.73)	85 (77.27)
29	López-Cortés et al., 2012	16 (53.33)	14 (46.67)	9 (50.00)	9 (50.00)
30	Naggie et al., 2012	8 (66.67)	4 (33.33)	7 (21.88)	25 (78.13)
31	Rallón et al., 2011	65 (61.90)	40 (38.10)	21 (23.08)	70 (76.92)
32	Dayyeh et al., 2011	8 (38.10)	13 (61.90)	2 (22.22)	7 (77.78)
33	Labarga et al., 2011	16 (66.67)	8 (33.33)	13 (34.21)	25 (65.79)
34	Nattermann et al., 2010	53 (56.38)	41 (43.62)	38 (38.78)	60 (61.22)
35	Rallón et al., 2010	56 (62.22)	34 (37.78)	19 (25.68)	55 (74.32)
36	Pineda et al., 2010	48 (62.34)	29 (37.66)	20 (25.97)	57 (74.03)

rs12979860		**RVR**		**Non RVR**	
		CC (%)	**Non CC (%)**	**CC (%)**	**Non CC (%)**
1	Matas et al., 2014	4 (66.67)	2 (33.33)	15 (29.41)	36 (70.59)
2	Corchado et al., 2014	15 (65.22)	8 (34.78)	64 (39.02)	100 (60.98)
3	Torres-Cornejo et al., 2014	41 (37.96)	67 (62.04)	2 (33.33)	4 (66.67)
4	Rivero-Juarez et al., 2013	19 (54.29)	16 (45.71)	65 (38.01)	106 (61.99)
5	Keane et al., 2013	37 (60.66)	24 (39.34)	28 (31.82)	60 (68.18)
6	Mandorfer et al., 2013	57 (44.19)	72 (55.81)	59 (34.71)	111 (65.29)
7	Neukam et al., 2013	19 (65.52)	10 (34.48)	40 (30.53)	91 (69.47)
8	Rivero-Juarez et al., 2012	20 (55.56)	16 (44.44)	12 (23.53)	39 (76.47)
9	Stenkvist et al., 2012	4 (66.67)	2 (33.33)	2 (28.57)	5 (71.43)
10	López-Cortés et al., 2012	11 (37.93)	18 (62.07)	14 (87.50)	2 (12.50)
11	Rivero-Juarez et al., 2012	22 (47.83)	24 (52.17)	15 (25.00)	45 (75.00)

12	Rallón et al., 2011	44 (69.84)	19 (30.16)	42 (31.58)	91 (68.42)
rs8099917		**SVR**		**Non SVR**	
		TT (%)	**Non TT (%)**	**TT (%)**	**Non TT (%)**
1	Lui et al., 2015	71 (82.56)	15 (17.44)	15 (46.87)	17 (53.13)
2	Bruno et al., 2015	37 (80.43)	9 (19.57)	21 (53.85)	18 (46.15)
3	Sticchi et al., 2015	11 (73.33)	4 (26.67)	42 (57.53)	31 (42.47)
4	de Castellarnau et al., 2012	66 (79.52)	17 (20.48)	60 (52.63)	54 (47.37)
5	Fernández-Rodríguez et al., 2012	135 (76.27)	42 (23.73)	69 (46.94)	78 (53.06)
6	Aparicio et al., 2010	56 (83.58)	11 (16.42)	48 (51.61)	45 (48.39)
rs12980275		**SVR**		**Non SVR**	
		AA (%)	**Non AA (%)**	**AA (%)**	**Non AA (%)**
1	Pineda-Tenor et al., 2014	26 (50.98)	25 (49.02)	23 (31.94)	49 (68.06)
2	Fernández-Rodríguez et al., 2014	44 (55.70)	35 (44.30)	31 (26.27)	87 (73.73)
3	Guzmán-Fulgencio et al., 2014	84 (52.50)	76 (47.50)	41 (28.47)	103 (71.53)
4	Fernández-Rodríguez et al., 2013	52 (55.91)	41 (44.09)	36 (27.91)	93 (72.09)
ss469415590		**SVR**		**NON SVR**	
		TT/TT (%)	**Non TT/TT (%)**	**TT/TT (%)**	**Non TT/TT (%)**
1	Franco et al., 2014	48 (65.75)	25 (34.25)	51 (38.06)	83 (61.94)
2	Sehgal et al., 2014	6 (85.71)	1 (14.29)	12 (85.71)	2 (14.29)
3	Real et al., 2014	66 (54.10)	56 (45.90)	34 (22.67)	116 (77.33)

Table 4 Genotypic frequencies for SVR rs12979860 HCV 1 OR 4

SL No:	Author, Year	SVR		Non SVR	
		CC	Non CC	CC	Non CC
1	Bruno et al., 2015	7 (70.00)	3 (30.00)	8 (27.59)	21 (72.41)
2	Labarga et al., 2015	65 (64.36)	36 (35.64)	43 (27.22)	115 (72.78)
3	Sticchi et al., 2015	9 (60.00)	6 (40.00)	20 (27.40)	53 (72.60)
4	Real et al., 2014	66 (54.10)	56 (45.90)	37 (24.67)	113 (75.33)
5	Sehgal et al., 2014	4 (57.14)	3 (42.86)	2 (14.29)	12 (85.71)
6	Franco et al., 2014	26 (66.67)	13 (33.33)	34 (31.78)	73 (68.22)
7	Corchado et al., 2014	54 (56.84)	41 (43.16)	37 (25.52)	108 (74.48)
8	Torres-Cornejo et al., 2014	32 (34.78)	60 (65.22)	11 (50.00)	11 (50.00)
9	Mandorfer et al., 2014	37 (48.05)	40 (51.95)	20 (33.90)	39 (66.10)
10	Neukam et al., 2013	44 (60.27)	29 (39.73)	35 (39.33)	54 (60.67)
11	Yingying et al., 2013	7 (70.00)	3 (30.00)	10 (38.46)	16 (61.54)
12	Zeremski et al., 2013	12 (44.44)	15 (55.56)	10 (16.39)	51 (83.61)
13	Rallon et al., 2013	5 (55.56)	4 (44.44)	5 (50.00)	5 (50.00)
14	Keane et al., 2013	57 (56.44)	44 (43.56)	8 (16.67)	40 (83.33)
15	Mandorfer et al., 2013	45 (47.87)	49 (52.13)	22 (29.33)	53 (70.67)
16	Amorosa et al., 2013	16 (47.06)	18 (52.94)	22 (22.92)	74 (77.08)
17	Di Lello et al., 2013	44 (57.14)	33 (42.86)	32 (23.53)	104 (76.47)
18	Neukam et al., 2013	33 (56.89)	25 (43.10)	26 (25.49)	76 (74.51)
19	Neukam et al., 2012	73 (59.35)	50 (40.65)	63 (26.47)	175 (73.53)
20	Osinusi et al., 2012	3 (33.33)	6 (66.67)	5 (38.46)	8 (61.54)
21	Rallón et al., 2012	36 (57.14)	27 (42.86)	15 (30.61)	34 (69.39)
22	Mira et al., 2012	12 (50.00)	12 (50.00)	6 (10.00)	54 (90.00)
23	de Castellarnau et al., 2012	56 (67.47)	27 (32.53)	42 (36.84)	72 (63.16)
24	Vispo et al., 2012	21 (52.50)	19 (47.50)	12 (21.43)	44 (78.57)
25	Naggie et al., 2012	8 (66.67)	4 (33.33)	7 (21.88)	25 (78.13)
26	Rallón et al., 2011	32 (56.14)	25 (43.86)	15 (19.23)	63 (80.77)
27	Nattermann et al., 2010	53 (56.38)	41 (43.62)	38 (38.78)	60 (61.22)
28	Rallón et al., 2010	26 (55.32)	21 (44.68)	14 (21.21)	52 (78.79)
29	Pineda et al., 2010	21 (63.64)	12 (36.36)	18 (25.71)	52 (74.29)

Table 5 Genotypic frequencies for SVR rs12979860 HCV 2 OR 3

SL No:	Author, Year	SVR		Non SVR	
		CC	Non CC	CC	Non CC
1	Bruno et al., 2015	19 (52.78)	17 (47.22)	5 (50.00)	5 (50.00)
2	Franco et al., 2014	20 (58.82)	14 (41.18)	18 (72.00)	7 (28.00)
3	Corchado et al., 2014	14 (77.78)	4 (22.22)	7 (77.78)	2 (22.22)
4	Zeremski et al., 2013	8 (47.06)	9 (52.94)	4 (57.14)	3 (42.86)
5	Mandorfer et al., 2013	39 (36.79)	67 (63.21)	10 (41.67)	14 (58.33)
6	Neukam et al., 2012	78 (66.67)	39 (33.33)	21 (51.22)	20 (48.78)
7	Stenkvist et al., 2012	5 (50.00)	5 (50.00)	1 (33.33)	2 (66.67)
8	López-Cortés et al., 2012	16 (53.33)	14 (46.67)	9 (50.00)	9 (50.00)
9	Rallón et al., 2011	33 (68.75)	15 (31.25)	6 (46.15)	7 (53.85)
10	Rallón et al., 2010	30 (44.78)	37 (55.22)	5 (35.71)	9 (64.29)
11	Pineda et al., 2010	26 (60.47)	17 (39.53)	2 (28.57)	5 (71.43)
12	Dayyeh et al., 2011	8 (38.10)	13 (61.90)	2 (22.22)	7 (77.78)

Table 6 Genotypic frequencies for SVR rs12979860 HCV 1

SL No:	Author, Year	SVR		Non SVR	
		CC	Non CC	CC	Non CC
1	Real et al., 2014	52 (55.32)	42 (44.68)	32 (26.23)	90 (73.77)
2	Sehgal et al., 2014	4 (57.14)	3 (42.86)	2 (14.29)	12 (85.71)
3	Corchado et al., 2014	43 (58.90)	30 (41.10)	36 (31.58)	78 (68.42)
4	Torres-Cornejo et al., 2014	32 (34.78)	60 (65.22)	11 (50.00)	11 (50.00)
5	Mandorfer et al., 2014	37 (48.05)	40 (51.95)	20 (33.90)	39 (66.10)
6	Yingying et al., 2013	7 (70.00)	3 (30.00)	10 (38.46)	16 (61.54)
7	Rallon et al., 2013	4 (66.67)	2 (33.33)	4 (44.44)	5 (55.56)
8	Keane et al., 2013	57 (56.44)	44 (43.56)	8 (16.67)	40 (83.33)
9	Amorosa et al., 2013	16 (47.06)	18 (52.94)	22 (22.92)	74 (77.08)
10	Neukam et al., 2013	33 (56.89)	25 (43.10)	26 (25.49)	76 (74.51)
11	Neukam et al., 2012	59 (59.00)	41 (41.00)	61 (30.05)	142 (69.95)
12	Osinusi et al., 2012	3 (33.33)	6 (66.67)	5 (38.46)	8 (61.54)
13	de Castellarnau et al., 2012	56 (67.47)	27 (32.53)	42 (36.84)	72 (63.16)

14	Vispo et al., 2012	21 (52.50)	19 (47.50)	12 (21.43)	44 (78.57)
15	Naggie et al., 2012	8 (66.67)	4 (33.33)	7 (21.88)	25 (78.13)
16	Nattermann et al., 2010	53 (56.38)	41 (43.62)	38 (38.78)	60 (61.22)
17	Rallón et al., 2010	22 (55.00)	18 (45.00)	12 (21.82)	43 (78.18)
18	Pineda et al., 2010	17 (68.00)	8 (32.00)	17 (29.82)	40 (70.18)

Table 7 Genotypic frequencies for SVR rs12979860 HCV 3

SL No:	**Author, Year**	**SVR**		**Non SVR**	
		CC	**Non CC**	**CC**	**Non CC**
1	Franco et al., 2014	20 (58.82)	14 (41.18)	18 (72.00)	7 (28.00)
2	López-Cortés et al., 2012	16 (53.33)	14 (46.67)	9 (50.00)	9 (50.00)
3	Rallón et al., 2010	30 (44.78)	37 (55.22)	5 (35.71)	9 (64.29)
4	Pineda et al., 2010	26 (60.47)	17 (39.53)	2 (28.57)	5 (71.43)

Table 8 Genotypic frequencies for SVR rs12979860 HCV 4

SL No:	**Author, Year**	**SVR**		**Non SVR**	
		CC	**Non CC**	**CC**	**Non CC**
1	Real et al., 2014	14 (50.00)	14 (50.00)	3 (10.71)	25 (89.29)
2	Corchado et al., 2014	11 (50.00)	11 (50.00)	1 (3.23)	30 (96.77)
3	Rallon et al., 2013	1 (33.33)	2 (66.67)	1 (100.00)	0 (0.00)
4	Neukam et al., 2012	14 (60.87)	9 (39.13)	2 (5.71)	33 (94.29)
5	Mira et al., 2012	12 (50.00)	12 (50.00)	6 (10.00)	54 (90.00)
6	Rallón et al., 2010	4 (57.14)	3 (42.86)	2 (18.18)	9 (81.82)
7	Pineda et al., 2010	4 (50.00)	4 (50.00)	1 (7.69)	12 (92.31)

Table 9 Genotypic frequencies for RVR rs12979860 HCV 1 /4

SL No:	**Author, Year**	**RVR**		**Non RVR**	
		CC	**Non CC**	**CC**	**Non CC**
1	Corchado et al., 2014	15 (65.22)	8 (34.78)	64 (39.02)	100 (60.98)
2	Torres-Cornejo et al., 2014	41 (37.96)	67 (62.04)	2 (33.33)	4 (66.67)
3	Keane et al., 2013	37 (60.66)	24 (39.34)	28 (31.82)	60 (68.18)
4	Mandorfer et al., 2013	25 (55.56)	20 (44.44)	42 (33.87)	82 (66.13)

5	Neukam et al., 2013	19 (65.52)	10 (34.48)	40 (30.53)	91 (69.47)
6	Rivero-Juarez et al., 2013	19 (54.29)	16 (45.71)	65 (38.01)	106 (61.99)
7	Rivero-Juarez et al., 2012	20 (55.56)	16 (44.44)	12 (23.53)	39 (76.47)

Table 10 Genotypic frequencies for RVR rs12979860 HCV 2 /3

SL No:	**Author, Year**	**RVR**		**Non RVR**	
		CC	**Non CC**	**CC**	**Non CC**
1	Mandorfer et al., 2013	32 (38.10)	52 (61.90)	17 (36.96)	29 (63.04)
2	Stenkvist et al., 2012	4 (66.67)	2 (33.33)	2 (28.57)	5 (71.43)
3	López-Cortés et al., 2012	11 (37.93)	18 (62.07)	14 (87.50)	2 (12.50)
4	Rivero-Juarez et al., 2012	22 (47.83)	24 (52.17)	15 (25.00)	45 (75.00)

Table 11 Genotypic frequencies for RVR rs12979860 HCV 1

SL No:	**Author, Year**	**RVR**		**Non RVR**	
		CC	**Non CC**	**CC**	**Non CC**
1	Corchado et al., 2014	15 (65.22)	8 (34.78)	64 (39.02)	100 (60.98)
2	Torres-Cornejo et al., 2014	41 (37.96)	67 (62.04)	2 (33.33)	4 (66.67)
3	Keane et al., 2013	37 (60.66)	24 (39.34)	28 (31.82)	60 (68.18)
4	Rivero-Juarez et al., 2013	19 (54.29)	16 (45.71)	65 (38.01)	106 (61.99)
5	Neukam et al., 2013	19 (65.52)	10 (34.48)	40 (30.53)	91 (69.47)
6	Rivero-Juarez et al., 2012	20 (55.56)	16 (44.44)	12 (23.53)	39 (76.47)

Table 12 Genotypic frequencies for SVR rs8099917 HCV 1 /4

SL No:	**Author, Year**	**SVR**		**Non SVR**	
		TT	**Non TT**	**TT**	**Non TT**
1	Bruno et al., 2015	9 (90.00)	1 (10.00)	14 (48.28)	15 (51.72)
2	Sticchi et al., 2015	11 (73.33)	4 (26.67)	42 (57.53)	31 (42.47)

3	de Castellarnau et al., 2012	66 (79.52)	17 (20.48)	60 (52.63)	54 (47.37)
4	Fernández-Rodríguez et al., 2012	70 (76.09)	22 (23.91)	57 (44.19)	72 (55.81)
5	Aparicio et al., 2010	33 (86.84)	5 (13.16)	35 (46.05)	41 (53.95)

Table 13 Genotypic frequencies for SVR rs8099917 HCV 2 /3

SL No:	Author, Year	SVR		Non SVR	
		TT	Non TT	TT	Non TT
1	Lui et al., 2015	71 (82.56)	15 (17.44)	15 (46.87)	17 (53.13)
2	Bruno et al., 2015	9 (90.00)	1 (10.00)	14 (48.28)	15 (51.72)
3	Aparicio et al., 2010	33 (86.84)	5 (13.16)	35 (46.05)	41 (53.95)

Table 14 Detailed genotypic frequencies for SVR rs12979860 all HCV subtypes

No:	Author, Year	SVR			Non SVR		
		CC	CT	TT	CC	CT	TT
1	Sticchi et al., 2015	9 (60.00)	4 (26.67)	2 (13.33)	20 (27.40)	40 (54.79)	13 (17.81)
2	Real et al., 2014	66 (54.10)	46 (37.70)	10 (8.20)	37 (24.67)	86 (57.33)	27 (18.00)
3	Sehgal et al., 2014	4 (57.14)	2 (28.57)	1 (14.29)	2 (14.29)	10 (71.43)	2 (14.29)
4	Franco et al., 2014	46 (63.01)	23 (31.51)	4 (5.48)	53 (39.55)	62 (46.27)	19 (14.18)
5	Yingying et al., 2013	7 (70.00)	3 (30.00)	0 (0.00)	10 (38.46)	10 (38.46)	6 (23.08)
6	Zeremski et al., 2013	20 (45.45)	17 (38.64)	7 (15.91)	14 (20.59)	38 (55.88)	16 (23.53)
7	Rallon et al., 2013	5 (55.56)	4 (44.44)	0 (0.00)	5 (50.00)	5 (50.00)	0 (0.00)
8	Keane et al., 2013	57 (56.44)	38 (37.62)	6 (5.94)	8 (16.67)	32 (66.67)	8 (16.67)
9	Amorosa et al., 2013	16 (47.06)	17 (50.00)	1 (2.94)	22 (28.21)	34 (43.59)	22 (28.21)
10	de Castellarnau et al., 2012	56 (67.47)	23 (27.71)	4 (4.82)	42 (36.84)	54 (47.37)	18 (15.79)
11	Nattermann et al., 2010	53 (56.38)	37 (39.36)	4 (4.26)	38 (36.54)	57 (54.81)	9 (8.65)

Table 15 Detailed genotypic frequencies for SVR rs12979860 HCV 1 /4

No:	Author, Year	SVR			Non SVR		
		CC	**CT**	**TT**	**CC**	**CT**	**TT**
1	Sticchi et al.,2015	9 (60.00)	4 (26.67)	2 (13.33)	20 (27.40)	40 (54.79)	13 (17.81)
2	Real et al.,2014	66 (54.10)	46 (37.70)	10 (8.20)	37 (24.67)	86 (57.33)	27 (18.00)
3	Sehgal et al.,2014	4 (57.14)	2 (28.57)	1 (14.29)	2 (14.29)	10 (71.43)	2 (14.29)
4	Franco et al.,2014	26 (66.67)	12 (30.77)	1 (2.56)	34 (31.78)	57 (53.27)	16 (14.95)
5	Yingying et al.,2013	7 (70.00)	3 (30.00)	0 (0.00)	10 (38.46)	10 (38.46)	6 (23.08)
6	Zeremski et al.,2013	12 (44.44)	10 (37.04)	5 (18.52)	10 (16.39)	36 (59.02)	15 (24.59)
7	Rallon et al.,2013	5 (55.56)	4 (44.44)	0 (0.00)	5 (50.00)	5 (50.00)	0 (0.00)
8	Keane et al.,2013	57 (56.44)	38 (37.62)	6 (5.94)	8 (16.67)	32 (66.67)	8 (16.67)
9	Amorosa et al.,2013	16 (47.06)	17 (50.00)	1 (2.94)	22 (28.21)	34 (43.59)	22 (28.21)
10	de Castellarnau et al.,2012	56 (67.47)	23 (27.71)	4 (4.82)	42 (36.84)	54 (47.37)	18 (15.79)
11	Nattermann et al.,2010	53 (56.38)	37 (39.36)	4 (4.26)	38 (36.54)	57 (54.81)	9 (8.65)

Table 16 Detailed genotypic frequencies for SVR rs12979860 HCV 2 /3

		SVR			Non SVR		
		CC	**CT**	**TT**	**CC**	**CT**	**TT**
1	Sehgal et al.,2014	4 (57.14)	2 (28.57)	1 (14.29)	2 (14.29)	10 (71.43)	2 (14.29)
2	Yingying et al.,2013	7 (70.00)	3 (30.00)	0 (0.00)	10 (38.46)	10 (38.46)	6 (23.08)
3	Rallon et al.,2013	4 (66.67)	2 (33.33)	0 (0.00)	4 (44.44)	5 (55.56)	0 (0.00)
4	Keane et al.,2013	57 (56.44)	38 (37.62)	6 (5.94)	8 (16.67)	32 (66.67)	8 (16.67)
5	Amorosa et al.,2013	16 (47.06)	17 (50.00)	1 (2.94)	22 (28.21)	34 (43.59)	22 (28.21)
6	de Castellarnau et al.,2012	56 (67.47)	23 (27.71)	4 (4.82)	42 (36.84)	54 (47.37)	18 (15.79)
7	Nattermann et al.,2010	53 (56.38)	37 (39.36)	4 (4.26)	38 (36.54)	57 (54.81)	9 (8.65)

Table 17 Summary OR from *IL28B* study

Genetic contrasts	Subgroup analysis based on HCV subtypes	No. of studies	Alleles/ Genotypes (n)	Random effects [OR (95% CI)]	Random effects P value	I^2 (%)	Q test P value	Egger Bias P value
SVR rs12979860								
CC vs. Non CC	All HCV subtypes	36	5182	3.26 (2.77, 3.84)	<**0.0001**	36.9	**0.015**	0.475
	HCV 1 or 4	29	3900	3.44 (2.87, 4.12)	<**0.0001**	32.7	**0.047**	0.988
	HCV 2 or 3	12	727	1.31 (0.92, 1.88)	0.1308	0	0.705	0.85
	HCV 1	18	2195	3.06 (2.37, 3.94)	<**0.0001**	38.4	**0.049**	0.913
	HCV 3	4	238	1.16 (0.58, 2.31)	0.6726	17.1	0.306	0.135
	HCV 4	7	294	10.22 (4.99, 20.92)	<**0.0001**	10.1	0.352	0.4
CC vs. TT	All HCV subtypes	11	769	4.75 (3.14, 7.18)	<**0.0001**	0	0.92	0.944
	HCV 1 or 4	11	709	5.20 (3.34, 8.10)	<**0.0001**	0	0.899	0.826
	HCV 1	7	404	5.95 (3.16, 11.19)	<**0.0001**	0	0.778	0.845
C vs. T	All HCV subtypes	11	2822	2.33 (1.97, 2.77)	<**0.0001**	0	0.878	0.926
	HCV 1 or 4	11	2652	2.43 (2.04, 2.91)	<**0.0001**	0	0.835	0.901
	HCV 1	7	1456	2.48 (1.95, 3.15)	<**0.0001**	0	0.719	0.628
(CC+CT) vs. TT	All HCV subtypes	11	1411	2.54 (1.73, 3.73)	<**0.0001**	0	0.838	0.805
	HCV 1 or 4	11	1326	2.60 (1.73, 3.93)	<**0.0001**	0	0.745	0.667
	HCV 1	7	728	3.18 (1.75, 5.76)	**0.0001**	0	0.675	0.865
CC vs. CT vs. TT	All HCV subtypes	11	1411	2.33 (1.83, 2.97)	<**0.0001**	0	0.99	0.926
	HCV 1 or 4	11	1326	2.43 (1.89, 3.13)	<**0.0001**	0	0.984	0.901
	HCV 1	7	728	2.48 (1.77, 3.48)	<**0.0001**	0	0.933	0.628

RVR rs12979860								
CC vs. Non CC	All HCV subtypes	12	1619	2.48 (1.59, 3.85)	<**0.0001**	63.8	**0.001**	0.841
	HCV 1 or 4	7	1072	2.86 (2.09,3.91)	<**0.0001**	0	0.699	0.642
	HCV 2 or 3	4	294	1.04 (0.28, 3.93)	0.9502	80.2	**0.002**	0.736
	HCV 1	6	903	2.97 (2.09, 4.23)	<**0.0001**	0	0.61	0.548
SVR rs8099917								
TT vs. Non TT	All HCV subtypes	6	972	3.78 (2.81, 5.07)	<**0.0001**	0	0.845	0.781
	HCV 1 or 4	5	659	4.02 (2.76, 5.86)	<**0.0001**	0	0.479	0.613
	HCV 2 or 3	3	131	1.94 (0.79, 4.76)	0.1465	0	0.39	ND
ss469415590								
TT vs. ΔG	All HCV subtypes	3	1000	2.46 (1.85, 3.28)	<**0.0001**	0	0.621	ND
TT/TT vs. ΔG/ΔG	All HCV subtypes	3	283	4.77 (2.49, 9.13)	<**0.0001**	0	0.461	ND
TT/TT vs. ((TT+ΔG)+(ΔG/ΔG))	All HCV subtypes	3	500	3.50 (2.37, 5.16)	<**0.0001**	0	0.52	ND
((TT/TT)+(TT+ΔG)) VS. (ΔG/ΔG)	All HCV subtypes	3	500	2.63 (1.43, 4.86)	**0.0019**	0	0.741	ND
(TT/TT) vs.(TT+ΔG) VS. (ΔG/ΔG)	All HCV subtypes	3	500	2.46 (1.65, 3.69)	<**0.0001**	0	0.788	ND
rs12980275								
AA vs. Non AA	All HCV subtypes	4	846	2.96 (2.22, 3.94)	<**0.0001**	0	0.775	0.698

Table 18 Characteristics of the studies involving IFITM3 gene.

First author, year	Population	Severity	Case	Control (Control type)	Detection method	Influenza Strain
Carter, 2017	European	severe	180	10013 (NHC)	PCR and Sanger sequencing	H3N2, H1N1 pdm09, H1N1, IBV
Pan, 2017	Chinese	severe, mild	245	65 (NHC)	RT-PCR and HRM assay	H1N1 pdm09, H3N2, IBV
Randolph, 2017	European	severe	185	503 (1000 G)	nested PCR, RT-PCR and sequencing	not specified
Lee, 2017	Chinese	severe	275	504 (1000 G)	PCR and Sanger sequencing	H7N9, H1N1 pdm09
David, 2017	Portuguese	severe, mild	41	200 (NHC)	RT-PCR and sequencing	H1N1 pdm09
Mehrbod, 2017	Iranian	mild	79	125 (NHC)	RT-PCR and sequencing	not specified
López-Rodríguez, 2016	White Spanish	severe, mild	118	246 (NHC)	RT-PCR and RFLP	H1N1 pdm09
Gaio, 2016	Portuguese	severe, mild	268	351 (NHC)	RT-PCR and RFLP	H1N1 pdm09
Wang, 2013	Chinese	severe	16	504 (1000 G)	RT-PCR and sequencing	H7N9
Mills, 2013	Caucasian, UK	severe, mild	293	2623 (NHC)	RT-PCR and Sanger sequencing	H1N1
Zhang, 2013	Chinese	severe, mild	83	504 (1000 G)	PCR	H1N1
Everitt, 2012	Caucasian,UK	severe	53	503 (1000 G)	Nested PCR and Sanger sequencing	H1N1, seasonal influenza

Table 19 The distribution of the IFITM3 rs12252 genotypes and allele frequency in influenza patients and controls

First author, year	Population	Distribution of rs-12252 genotypes						Frequency of rs-12252 alleles			
		TT		CT		CC		T		C	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Severe infection											
Carter, 2017	Whites	170 (94.4)	9412 (94.0)	9 (5.0)	597 (6.0)	1 (0.6)	4 (0.0)	174 (96.7)	9715 (97.0)	6 (3.3)	298 (3.0)
Pan, 2017	East Asians	14 (8.5)	16 (24.6)	49 (29.9)	34 (52.3)	101 (61.6)	15 (23.1)	77 (23.5)	66 (50.8)	251 (76.5)	64 (49.2)
Randolph, 2017	Whites	173 (93.5)	462 (91.8)	10 (5.4)	41 (8.2)	2 (1.1)	0 (0)	7 (3.8)	965 (95.9)	178 (96.2)	41 (4.1)
Lee, 2017	East Asians	62 (22.5)	123 (24.4)	115 (41.8)	230 (45.6)	98 (35.6)	151 (30)	120 (43.5)	476 (47.2)	155 (56.5)	532 (52.8)
David,2017	Whites	18 (81.8)	176 (88)	4 (18.2)	24 (12)	0 (0.0)	0 (0.0)	40 (90.9)	376 (94)	4 (9.1)	24 (6)
López-Rodríguez, 2016	Whites	53 (88.3)	229 (93.1)	7 (11.7)	17 (6.9)	0 (0.0)	0 (0.0)	113 (94.2)	475 (96.5)	7 (5.8)	17 (3.5)
Gaio,2016	Whites	73 (86.9)	312 (88.9)	9 (10.7)	38 (10.8)	2 (2.4)	1 (0.28)	155 (92.3)	662 (94.3)	13 (7.7)	40 (5.7)
Wang,2014	East Asians	3 (18.8)	123 (24.4)	7 (43.7)	230 (45.6)	6 (37.5)	151 (30)	13 (40.6)	476 (47.2)	19 (59.4)	532 (52.8)
Mills, 2013	Whites	31 (91.2)	2417 (92.2)	3 (8.8)	202 (7.7)	0 (0.0)	4 (0.1)	65 (95.6)	5036 (96.0)	3 (4.4)	210 (4.0)
Zhang, 2013	East Asians	2 (6.2)	123 (24.4)	8 (25)	230 (45.6)	22 (68.8)	151 (30)	12 (18.8)	476 (47.2)	52 (81.2)	532 (52.8)

Everitt, 2012	Whites	46 (86.8)	462 (91.8)	4 (7.5)	41 (8.2)	3 (5.7)	0 (0)	96 (90.6)	965 (95.9)	10 (9.4)	41 (4.1)
Mild infection											
Pan, 2017	East Asians	14 (17.3)	16 (24.6)	45 (55.6)	34 (52.3)	22 (27.2)	15 (23.1)	73 (45.1)	66 (50.8)	89 (54.9)	64 (49.2)
David, 2017	Whites	16 (84.2)	176 (88)	2 (10.5)	24 (12)	1 (5.3)	0 (0)	34 (89.5)	376 (94)	4 (10.5)	24 (6)
Mehrbod, 2017	Whites	67 (84.8)	120 (96.0)	9 (11.4)	4 (3.2)	3 (3.8)	1 (0.8)	143 (90.5)	244 (97.6)	15 (9.5)	6 (2.4)
López-Rodríguez, 2016	Whites	51 (88.0)	229 (93.1)	6 (10.3)	17 (6.9)	1 (1.7)	0 (0.0)	108 (93.1)	475 (96.5)	8 (6.9)	17 (3.5)
Gaio, 2016	Whites	152 (82.6)	312 (88.9)	32 (17.4)	38 (10.8)	0 (0)	1 (0.28)	336 (91.3)	662 (94.3)	32 (8.7)	40 (5.7)
Mills, 2013	Whites	235 (90.7)	2417 (92.1)	22 (8.5)	202 (7.7)	2 (0.8)	4 (0.2)	492 (95.0)	5036 (96.0)	26 (5.0)	210 (4.0)
Zhang, 2013	East Asians	7 (13.7)	123 (24.4)	31 (60.8)	230 (45.6)	13 (25.5)	151 (30)	45 (44.1)	476 (47.2)	57 (55.9)	532 (52.8)

Table 20 Summary Odds ratio from study of the IFITM3 polymorphism

Genetic Contrasts	Population and subgroup analysis	Studies (*n*)	Alleles/ Genotypes (*n*)	Random effects [OR(95% CI)]	Random effects *P* value	I^2 (%)	Q test *P* value	Egger Bias P value
C vs. T	Severe all	11	30814	1.69 (1.23, 2.33)	**0.001**	60.7	**0.005**	0.92
	Mild all	7	8888	1.46 (1.13, 1.87)	**0.004**	23.5	0.25	0.04
	Severe all vs. Mild all	6	2096	1.47 (0.82, 2.63)	0.192	67.3	**0.009**	0.149
	Severe Whites	7	29108	1.35 (1.00, 1.83)	**0.048**	0	0.494	0.868
	Severe East Asians	4	1706	2.21 (1.22, 4.03)	0.009	82	**0.0008**	0.504
	Mild Whites	4	7880	1.48 (1.11, 1.97)	**0.007**	0	0.724	0.184
	Mild East Asians	2	600	1.17 (0.84, 1.63)	0.353	0	0.662	ND
CC vs. TT	Severe all	11	14075	4.21 (2.15, 8.22)	**<0.0001**	27.9	**0.179**	0.145
	Mild all	7	3921	1.99 (1.05, 3.77)	**0.036**	0	0.797	0.292
	Severe all vs. Mild all	6	830	4.69 (2.16, 10.17)	**<0.0001**	0	0.85	0.29
	Severe Whites	7	13589	9.92 (2.45, 40.15)	**0.001**	0	0.988	0.711
	Severe East Asians	4	486	3.61 (1.36, 9.59)	0.01	71	**0.016**	0.422
	Mild Whites	4	3597	5.28 (0.97, 28.78)	0.054	0	0.941	0.618
	Mild East Asians	2	133	1.50 (0.73, 3.10)	0.273	0	0.738	ND
(CC+CT) vs. TT	Severe all	11	15407	1.40 (1.06, 1.85)	**0.016**	13.5	0.316	0.357
	Mild all	7	4444	1.54 (1.18, 2.01)	**0.001**	0	0.544	0.22
	Severe all vs. Mild all	6	1048	1.19 (0.77, 1.85)	0.421	3.9	0.392	0.751
	Severe Whites	7	14554	1.18 (0.85, 1.63)	0.315	0	0.704	0.419
	Severe East Asians	4	853	1.99 (1.07, 3.70)	0.029	44.4	**0.145**	0.468
	Mild Whites	4	3940	1.43 (1.05, 1.94)	**0.021**	0	0.727	0.628
	Mild East Asians	2	300	1.50 (0.81, 2.77)	0.193	0	0.881	ND

CC vs. (CT+TT)	Severe all	11	15407	3.76 (2.03, 6.96)	**<0.0001**	43.3	**0.062**	0.206
	Mild all	7	4444	1.35 (0.82, 2.23)	0.24	0	0.564	0.216
	Severe all vs. Mild all	6	1048	4.72 (2.86, 7.78)	**<0.0001**	0	0.833	0.404
	Severe Whites	7	14554	9.80 (2.42, 39.62)	**0.001**	0	0.987	0.741
	Severe East Asians	4	853	3.16 (1.42, 7.01)	0.005	78.4	**0.003**	0.487
	Mild Whites	4	3940	5.22 (0.96, 28.46)	0.056	0	0.946	0.615
	Mild East Asians	2	300	1.10 (0.64, 1.88)	0.739	0	0.643	ND

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