Author’s response to reviews

Title: Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients

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Version: 4 Date: 5 October 2012

Author's response to reviews: see over
Dear Sir/Madam,

Thank you very much for your e-mail of June 29, 2012. Please find enclosed a point-by-point response to the reviewers’ comments and the new revised version of our manuscript. We hope that the current revised version of our manuscript is acceptable for publication. Please feel free to contact us regarding any further questions about our work.

As you can see, the literature search has been updated up to July 9th. As a consequence, a total of 282 studies have been reviewed and in the end 74 articles were included (26 new studies). A total of six articles that were included in the previous version have been replaced by others with higher number of patients.

We have considered all reviewers’ comments, and thus our study has been carefully updated with the aim of increasing its overall quality. We are very grateful to all reviewers for their valuable suggestions.

Thank you very much for your consideration. We look forward to hearing from you at your earliest convenience.

Yours sincerely,

Maria Angeles Jimenez-Sousa, PhD

Majadahonda, Friday, October 05, 2012

Manuscript ID: 1858302199718684
Title: Meta-analysis: implications of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients
Author(s): María A JIMÉNEZ-SOUSA*, Amanda FERNÁNDEZ-RODRÍGUEZ*, María GUZMÁN-FULGENCIO, Mónica GARCÍA-ÁLVAREZ, Salvador RESINO, PhD.
Jimenez-Sousa et al. performed meta-analysis to assess the impact of IL28B polymorphisms (SNPs) on treatment outcome and spontaneous viral clearance of HCV infection. The effect of the SNPs on the course of infection depends on ethnicity, HCV genotype and type of viral infection. In Caucasian, the SNPs rs12979860 and rs8099917 are the best genetic markers for treatment-related and spontaneous viral clearance, while in Asian the SNP rs12980275 is also important. No differences between HCV mono- and HCV/HIV co-infected patients were observed.

The manuscript is at great length and well written. It provides an overview of current literature and discusses the reported findings in the context of the present knowledge. I have a few concerns:

Major Compulsory Revisions

1. There is a discrepancy in the time range papers where collected for the meta-analysis. Authors state, that “….this report is based on published data prior to October 18, 2011….” But “…years of studies ranged from 2009 to 2012….”. For example, the report from de Nicola et al. was primarily published January 2012, Beinhardt in November 2011. The authors need to clarify the publication time range and to set a clear deadline.

At the beginning, the literature search included all accepted articles up to October 18, 2011. However, some articles had been accepted and appeared as “Epub ahead of print” in Pubmed, at that time. Therefore, the final publication date was, in some cases, subsequently updated to 2012.

2. Currently, new relevant reports were published dealing with large patient cohorts. We clearly recommend to include these new findings into the meta-analysis. Therefore, literature search should be updated to 2012.

We have updated our study, and therefore the literature search has been performed up to July 9th, 2012. As a consequence, 124 new studies were potentially relevant for our study (282 in total) and finally 67 were included for SVR and 10 for SC.

“The literature search identified 282 publications (Figure 1). After initial screening and removal of duplicates (n= 1), 207 articles were rejected based on the title/abstract (n= 82) and the full text (n= 125), because they did not meet the inclusion criteria. This left 74 studies that were eligible for inclusion (Supplemental Table 1), comprised of 67 that were selected for SVR meta-analysis [5, 9-11, 25-87] and 10 for SC meta-analysis [26, 28, 65, 88-94]. Three studies were included in both analyses [26, 28, 65].”
3. Recently, two meta-analyses were already published by Li et al. (2011 Hepatitis Monthly) and Chen et al. (2012, Alimentary Pharmacology and Therapeutic) which should be discussed. One of the meta-analysis studies referenced in our study was the Li et al. study. We have completed the discussion section with the work of Chen and two less completed meta-analyses that have been recently published (Shi et al., 2012; Schreiber et al., 2012).

We have modified the following paragraph in discussion:

To our knowledge, to date a total of five reviews containing data from meta-analyses have been published about the relationship between IL28B polymorphisms and SVR [96-100]. Romero-Gomez et al. and Li et al. reports are limited since they involve literature searches up to January and May 2010, respectively, leading to the selection of a low number of studies in both cases (only 7 studies). In addition, all meta-analyses were only performed for rs12979860 and rs8099917. The other three meta-analyses were broader, ranging from 17 to 36 studies. All of them only analysed the effect of the IL28B polymorphisms rs12979860 and rs8099917 on SVR by ethnicity and HCV genotype, although the study by Scheiber et al. was limited to HCV genotype 2 and 3. However, the literature searches of these meta-analyses only included publications up to the end of 2011

4. The authors found high heterogeneity between the studies of rs12979860, rs8099917 and 12980275. What are the sources of this study-between heterogeneity? Identification of outliers would be interesting.

The sources of between-study heterogeneity have been studied by subgroup analysis and meta-regression [1, 2].


As it was described in Statistical analysis section (page 7):

“The heterogeneity of each group of ORs was assessed by χ² test, which suggests the presence of heterogeneity when p-values are less than 0.1. Heterogeneity was quantified with the I² metric, which provides a measure of the degree of inconsistency in the studies' results (I² >50% indicated considerable heterogeneity). When significant heterogeneity existed, a random effect model (the DerSimonian and Laird method [19]), was applied; and a subgroup meta-analysis and forest plot based on ethnicity, HCV genotype and coinfecion data (HCV or HCV/HIV) were performed in order to identify the effect modifiers [20].”

“In addition, when heterogeneity was detected, meta-regression analysis was also performed with the aim of defining the potential effect of the covariates on spontaneous or treatment-related clearance.”
In this setting, we identified HCV genotype as a crucial cause of heterogeneity for rs12979860 along with HCV genotype, ethnicity and fibrosis for rs8099917 (pag. 11-13). On the other hand, according to the reviewer's suggestions, we have identified outliers of the heterogeneity. The Galbraith plot graphics were performed for this reason (Figure 4) and it was included in Statistical analysis section (page 7).

"Moreover, the Galbraith plot was used in order to detect possible outliers of the heterogeneity, which could have biased the combined estimate. This graphical method allowed those studies that had a strong influence on the pooled results to be checked [21, 22]. Trials outside the Galbraith limits were trials where the 95% confidence interval did not contain the pooled estimate."

rs12979860

"The pooled OR for overall data was 3.77 (95%CI= 3.25-4.37) and there was heterogeneity (p<0.001; I^2= 52.3%). When Galbraith plot was analysed two outliers of heterogeneity were identified (Thompson et al. [25] and Moghaddam et al. [11]) (Figure 4)."

rs8099917

"When Galbraith plot was carried out (Figure 4), six outliers of the heterogeneity were identified: five studies grouped together (all Asians with genotype 1 and mostly Japanese) and one study (Moghaddam et al. [11]), which was also an outlier for rs12979860 analysis."

"Meta-regression analysis allowed us to infer that the proportion of significant variance accounted for each different covariate: ethnicity (Caucasians vs. Asians: adj-R2= 26.00%; p=0.002), HCV genotype (adj-R2= 51.57%; p<0.001), and advanced fibrosis (adj-R2= 32.64%; p=0.016). Type of infection and baseline HCV viral load did not seem to influence the heterogeneity (p= 0.992 and p=0.087 respectively)."

In the case of rs12980275, we identified one outlier of the heterogeneity but the reduced number of studies prevents us from drawing firm conclusions about this statistical analysis. In fact, a Galbraith plot was not shown because less than ten studies were available.

"Galbraith plot showed Tanaka et al. [5] as an outlier of the heterogeneity (data not shown), however the reduced number of studies prevented us from drawing firm conclusions about this analysis."

Minor Essential Revisions

Figure legends:
1. Figure legends in the manuscript and the supplementary material are quite repetitive. I would recommend to use one main description and only to highlight the differences.
We agree with the reviewer. We have summarized all figure legends.

References:
1. Although the report of Moher et al. was published in 4 different journals (References 12, 18, 36 and 38), it is still remains the same study. There is no need to describe them separately.
   We agree with the reviewer. We have referred to only one study. We apologize for this mistake.

2. The references 29 (Hardwick et al.) and 30 (Vartanian et al.) do not report previous meta-analyses of IL28B. They rather deal with botanic gardens and JUNB degradation. What are the correct references?
   We apologize again for this mistake. We wanted to refer to Romero-Gómez et al. (2012), Liver Int and Li et al. (2011) Hepatitis Monthly.

   Romero-Gomez et al. and Li et al. reports are limited since they involve literature searches up to January and May 2010, respectively, leading to the selection of a low number of studies in both cases (only 7 studies). In addition, all meta-analyses were only performed for rs12979860 and rs8099917.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

REVIEWER 2:
Reviewer's report
Title: Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients
Version: 3 Date: 31 May 2012
Reviewer: Javier Salmeron

Reviewer's report:
Comment for authors
Title: “Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients”

COMMENTS:
The manuscript entitled “Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients” presents a large meta-analysis of those SNPs involved in the SVR and SC related to the patients infected with HCV.
In my opinion, the references are not following the same structure and the authors should revise them prior publication.
I would like to point out something that in my opinion it is extremely difficult to understand, the references 12, 18, 36 and 38 corresponds to the same article (same authors, same title, same content), published in different journals??; the same occurs with references 35 and 37. We apologize for all these mistakes; We have corrected them and all references have been revised.

Moreover, in my opinion the authors should cite in the section of results (page 9, lines 4-5) the 48 references used in the meta-analysis study. Even more, considering that these references appear in the section of bibliography.

The references have been included in the results section (page 9, section: Studies and data included in the meta-analysis). Moreover, we have also included a reference to Supplemental table 1 where all the studies have been described.

“….This left 74 studies that were eligible for inclusion (Supplemental Table 1), comprised of 67 that were selected for SVR meta-analysis [5, 9-11, 25-87] and 10 for SC meta-analysis [26, 28, 65, 88-94]. Three studies were included in both analyses [26, 28, 65]”.

The authors should also pay attention to the fact that the references 29 and 30 cited during the discussion do not correspond with the meta-analysis of the IL28B comment (these articles deals with botanic gardens and AP-1/mTOR/AKT, respectively).

We apologize again for this mistake. We wanted to refer to Romero-Gomez et al. (2012), Liver Int and Li et al. (2011) Hepatitis Monthly. This mistake has been corrected.

Romero-Gomez et al. and Li et al. reports are limited since they involve literature searches up to January and May 2010, respectively, leading to the selection of a low number of studies in both cases (only 7 studies). In addition, all meta-analyses were only performed for rs12979860 and rs8099917.

Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: None conflict

REVIEWER 3:
Reviewer’s report
Title: Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients
Version: 3 Date: 1 June 2012
Reviewer: Guangwen Cao

Reviewer’s report:
This is an interesting and well written paper with the aim to assess the associations between single nucleotide polymorphisms (SNPs) near the IL28B gene with sustained virologic response (SVR) and spontaneous clearance (SC).

Forty-three studies were included, and in total, 18499 patients were studied for SVR and 2281 for SC. The authors concluded that IL28B polymorphisms influence both IFN treatment outcome and natural clearance of HCV. There is not a universal predictor SNP identified. The best genetic markers appeared to be different with ethnicity, genotype or type of infection. The results could be highly useful for more precise treatment decision making. The methods in this paper are appropriately used and the data are well documented. Statistical analyses are sufficient detail and the results are reliable. But there are still some points need to be revised and illustrated.

Minors:

1. There are two reviews have been published about the relationship between IL28B polymorphisms and SVR. But the authors cited wrong articles. Please check carefully of 29 and 30 references.

   We apologize for this mistake. We have had problems with the reference editor software. We wanted to refer to Romero-Gómez et al. (2012), Liver Int and Li et al. (2011) Hepatitis Monthly. This mistake has been corrected.

   Romero-Gomez et al. and Li et al. reports are limited since they involve literature searches up to January and May 2010, respectively, leading to the selection of a low number of studies in both cases (only 7 studies). In addition, all meta-analyses were only performed for rs12979860 and rs8099917.

2. There are so many figures in this paper. The author should organize the results in good way to present them explicitly. For example, analysis results of subgroup can be presented in a table for the three SNPs of rs12979860, rs8099917 and rs12980275 by varying of ethnicity, genotype and type of infection.

   We agree with the reviewer. We have summarized all forest plots in Tables 1a and 1b, which will probably be more instructive to the reader. The forest plots have been changed to Supplementary material.

3. In conclusion section, authors use “the best genetic marker” to interpret the role of IL28B polymorphisms. It is hard to understand if author can not make reasonable explanation.

   We used this statement based on the results of the meta-analysis as we indicated in the conclusions. The reviewer is right that it is too strong of an assertion and therefore, we have modified this sentence due to not being able to provide a functional or biological explanation.

Conclusion section of Abstract:

“Depending on patient ethnicity, genotype or type of infection, the most adequate genetic markers appeared to be different”

Conclusion section of Discussion
“However, although we cannot provide a biological explanation, according to our findings the most adequate genetic marker seems to vary depending on ethnicity, HCV genotype, and type of viral infection.”

4. In supplemental figure 4, there are some markings that are misunderstanding, such as “Thompson et al (2010)a, Thompson et al (2010)b, Thompson et al (2010)c”. Could authors make some explanation on it.

We explained this nomenclature in Material and Methods section/Data extraction, page 6:

“When articles provided data from patients of different ethnicities, HCV genotypes and/or types of infection (HCV and HCV/HIV), the studies were divided into subgroups. Each subgroup was identified by a sequential letter”.

But we understand that some Supplemental figure legends are incomplete, thus we have included a new table explaining the meaning of each sequential letter (Supplemental Table 4), and a new sentence in Results section (page 10)

“When articles were divided into subgroups, each one was identified by a sequential letter (Supplemental Table 4).”

5. There two supplemental table 1, please revise.

We apologize for the mistake. The numbers have been corrected.

6. Figure 2 is not necessary to be used on this paper, but can be treated as supplementary file.(discretionary revision).

Figure 2 has been changed to Supplementary material as recommended by the reviewer (Supplemental Figure 2).

Quality of written English: Acceptable
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests: I declare that I have no competing interests

REVIEWER 4:
Reviewer's report
Title: Meta-analysis: implication of IL28B polymorphisms in spontaneous and treatment-related clearance for hepatitis C patients
Version: 3 Date: 29 June 2012
Reviewer: Jaime Peters

Reviewer's report:
The authors have undertaken a very large review of the evidence. Although there are many results reported, there needs to be more consideration of the studies and the assumptions
made in the analysis when reporting these results. Below are my suggestions for helping to improve the manuscript.

Major compulsory revisions
1. There are a lot of results and figures presented. The penultimate paragraph of the Discussion section clearly identifies the considerations needed to interpret the results of this meta-analysis. To help the reader fully acknowledge how the different reported results should be interpreted, as well as giving an idea of which ones we can place more confidence in, there should be more text to guide the reader through the Results section itself. For instance, p10 rs12979860 a) Race: It would be helpful to point out that three of these subgroup results are based on results from a very small number of studies, therefore there is uncertainty associated with the estimates reported. p11 rs12979860 b) HCV genotype: Point out that the difference between genotype 1/4 and 2/3 is statistically significant here. p11 rs8099917 a) Race: Make clear that there is still a great deal of heterogeneity within the Asian subgroup (i.e. I² = 66%). p11 rs8099917 b) HCV genotype: Some interpretation needed so reader can get an idea of how much confidence to place in these estimates. p11 rs8099917 c) Type of viral infection: As above, point out since heterogeneity within HCV monoinfected subgroup (I²=65%), only three studies in HCV/HIV coinfectd subgroup. p12 rs12980275 a) Race and b)HCV genotype: Point out only 2 or 3 studies in each subgroup.

We are really grateful for all reviewer comments and suggestions, and we have tried to address all of them. Regarding the high number of figures reported previously, we have summarized all of them in Tables 1a and Table 1b, and the forest plots have been changed to Supplemental material (Supplemental Figures 3-24).

We have also included interpretation of the results in every comparison in order to guide the reader.

2. The authors state that meta-analyses were conducted following PRISMA guidelines. PRISMA is for the reporting of systematic review and meta-analyses, not for conduct. The authors should check that their methods comply with guidelines for systematic review and meta-analysis methods such as Cochrane Handbook, Centre for Reviews and dissemination handbook, published texts (e.g. Sterne et al Systemati Reviews in Healthcare (BMJ Books) or Sutton et al Methods for Meta-analysis in Medical Research (Wiley)), the HuGENetTM HuGE, review handbook, specifically for meta-analyses of genetic association studies.

We wanted to say that our work was written following PRISMA guidelines, but we have modified this sentence in order to be precise. In addition, we have checked that our methods comply with guidelines for meta-analysis methods, so we have included a reference to Sutton et al.

"Meta-analysis was conducted following guidelines from Sutton et al. [12] and data have been reported following PRISMA guidelines[13]."

3. Related to point 2 above, there does not seem to be any report of critical appraisal of these studies. This is a serious omission as it is not clear to the reader whether the studies on which the meta-analyses are based are highly likely to be susceptible to bias or not. The authors should provide details on the quality of the included studies to aid interpretation of the meta-analysis results.
We appreciate the reviewer’s recommendation. Thus, we have performed a critical appraisal of all studies included in the meta-analysis, in which the reader can see those studies more susceptible to bias. These data are shown in Supplemental table 2 and 3.

Material and Methods section, (Page 6)

“Quality appraisal

In order to evaluate the quality of the included studies, two investigators appraised them independently using a checklist based on the GATE quality appraisal tool [16]. Each item was rated as +1 (well reported and reliable), 0 (unclear, insufficient detail provided) or -1 (poorly reported, not useful or reliable). The overall validity of each study was also rated by a similar system: +1 (most of the quality items were fulfilled), 0 (some criteria were not fulfilled), or -1 (few or none of the items were fulfilled).”

Results, Studies and data included in the meta-analysis

“Regarding the quality appraisal of the included studies for SVR, 21 were rated as +1, 43 as 0 and two as -1 (Supplemental Table 2). In the case of SC, four studies were rated as +1 and six as 0 (Supplemental Table 3).”

4. I suggest the authors be VERY careful about omitting studies just because they are different to the rest of the studies (p10, a) Sustained virologic response and p13 b) Spontaneous clearance). If the authors could supply an explanation for why these 2 studies should be excluded (Smith for SVR and Dring for SC) on the basis of population characteristics etc, I would be much more confident about this part of their methods. However, as it stands, I would advise the authors to report the results of these meta-analyses with Smith and Dring included, and report their influence sensitivity analyses after this. It is not good practice to exclude studies just because their estimates are different to the others. This practice could easily introduce bias into the meta-analysis and provide misleading results.

We have followed the guidelines of the reviewer. Based on our results and on the basis of population characteristics, we cannot supply any explanation for excluding Fischer for SVR and Dring for SC. Therefore, we have shown data including these studies, and we have commented on the results from the sensibility analysis. Additionally, we have shown the results from the statistical analysis excluding these studies.

(Note: Fischer et al. replaces Smith et al. in the new version due to the inclusion of a larger number of patients).

SVR, rs12980275 (Page 13-14)

“By sensitivity analysis (Figure 3), we observed that the Fischer et al. study [67] on rs12980275 apparently influenced the overall results, and thus a new statistical analysis was performed excluding Fischer et al. (data do not shown). This influence seemed to affect only genotype 1/4, where heterogeneity was reduced to 0%. Results for genotype 1/4 varied slightly (OR=9.13 (95%IC=5.84-14.26)), although the significance of the OR was not altered. Based on these results and on the
basis of population characteristics, we cannot offer any explanation for excluding the Fischer et al. study."

Spontaneous clearance, rs12979860 (page 15)
"Sensitivity analysis (Figure 3) showed that Dring et al. (2011) [88] could be influencing the overall statistical analysis. For this reason, we also analyzed the data after removing this study. Results were similar and the significance of OR was not altered. According to these results and to the population characteristics we could not provide any reason for excluding this study."

5. I am not convinced that excluding those SNPs where only one study provides evidence is appropriate. I realise that the focus of the paper is the meta-analysis, but this paper also represents the most-up-to-date review of the evidence in this area and so reporting these results, even though they can’t be included in a meta-analysis, would be very useful. For rs8099917, meta-analysis of only 2 studies is reported and I’m not sure this is any more informative than just reporting results from an individual study.
We have introduced two new figures with all available information for those SNPs where only one study provides evidence (Supplemental figures 19 and 25).

SVR, page 14
"We have also recorded all the polymorphisms that were studied in only one study each. A total of twelve SNPs have been reported with OR ranging from 1.19 to 9.96, however only eight were significant (rs35790907 (AA), rs12972991 (AA), rs12982533 (TT), rs688187 (GG), rs4803221 (CC), rs8109886 (CC), rs12980602 (TT) and rs4803219 (CC) (Supplemental figure 19))."

SC, Page 15
"Other SNPs
We have also recorded all the polymorphisms that were studied for SC in only one study each. A total of seven SNPs have been reported with OR ranging from 1.19 to 14.88, however only four of them (rs10853728 (CC), rs12980275 (AA), rs8105790 (TT), rs8103142 (TT)) were significant although most of them with very high confidence intervals (Supplemental figure 25)."

6. The methods section reports that searches were conducted up until October 2011, yet in the results section (p9) it is reported that publication year ranged from 2009 to 2012 – could the inclusion of 2012 articles be clarified by the authors?
At the beginning, the literature search included all accepted articles up to October 18, 2011. However, some articles had been accepted and appeared as “Epub ahead of print” in Pubmed, at that time. Therefore, the final publication date was, in some cases, subsequently updated to 2012. In any case, this problem has been solved as the literature search has been completed up to July 9th, 2012.
7. p10 Publication bias test results: I would also add in this section that it is very difficult to
tell whether publication bias is present for rs12979860 (SC) and rs12980275 (SVR) as there are
only a few studies reporting on these. Therefore, publication bias cannot be ruled out and this
should be made clear to readers.
Recommendations indicate that such methods should not be used when there are fewer than
10 studies (see Sterne et al BMJ 2011; 342: d4002 or Cochrane Handbook).
We have only shown publication bias test results for those SNPs with more than ten studies
(rs12979860 and rs8099917 for SVR). We have also included the following sentence in Publication
bias test results (page 10)
“Those SNPs found in less than ten articles should not be evaluated for publication bias, following
recommendations for correct funnel plot interpretations [95]. For that reason, publication bias was
only analysed for rs12979860 and rs8099917 in SVR.”

8. Related to 7 above, the authors should qualify their statements of publication bias not being
detected when only a handful of studies are included in the analyses. In particular, last
sentence of page 13: it should be pointed out that you would not expect to find publication
bias in a sample of 2 studies as the methods are not powerful enough (again see Sterne et al
BMJ).
We are very grateful for the clarification.
Following the reviewer’s recommendations, we have omitted the publication bias data for those
analyses including fewer than ten articles.

9. Bottom of page p15 “Both studies individually showed a significant association, but this
significance was lost after performing the meta-analysis” Could the authors provide an
explanation of why this is seen?
The probable explanation is the huge interval confidence provided by one study (Venegas et al),
which ranges from 3.5-231.05. This argument has been included in the last paragraph of the IL28B
and ethnicity section (page 18)
“This could be due to the extremely wide confidence interval of the Venegas et al.[9] study”

Minor essential revisions
2. Define IFN in abstract (Conclusions)
Ok

3. Main text suggests fixed and random effects meta-analysis models used, but abstract only
reports that random effects models were used – this should be clarified.
Both models were used. We clarify this in the Abstract section.
“Pooled odds ratios were estimated by fixed or random effects models when appropriate”.

4. p9, first line of second paragraph: use of “near IL28B” – the term “adjacent”
was used in the inclusion criteria section. Do near and adjacent mean the same in this
context? If so, perhaps one or other term could be used throughout for consistency.
As the reviewer sensed, both terms mean the same in this context. We used two terms in order to avoid repetition. The terminology has been adjusted so that only one word ("near") has been used throughout the text.

Discretionary revisions

1. p9, 3rd paragraph: providing the number of studies as well as the number of individuals for each genotypes could be helpful to the reader.
   This information has been completed in page 9, third paragraph.
   "The rs12979860 polymorphism involved 12184 patients from 42 studies, the rs8099917 was studied in 11839 patients from 39 studies, and the rs12980275 in 2786 patients from six studies Regarding SC analysis, 2340 patients from seven studies and 1783 from four reports".

2. p18, last paragraph: typographical error: - “row” should be “raw”.
   Ok.

Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests.