December 25, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6369-edited.doc).

Title: Polymorphisms of IFNL3/IL28B Gene and Hepatitis C: from Adults to Children

Authors: Giuseppe Indolfi, Chiara Azzari, Massimo Resti

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6369

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers. Following you will find a point by point explanation of the changes made.

Reviewer (1)

The reviewer suggested throughout the manuscript some minor grammatical changes that have been done.

On page 6, last sentence, the reviewer asked to explain briefly why "in treatment-experienced patients planned for boceprevir/telaprevir therapy, there is little utility for *IFNL3* genotyping once patients have been stratified for prior treatment response[22,24]."

R. According to the comment of the reviewer, the following sentence was added: "In the REALIZE study, for example, prior treatment response was the strongest predictor of treatment outcome, and no difference in SVR rate was seen according to *IFNL3* genotype when patients were considered on the basis of treatment history[24]."

On the last line of page 7, the reviewer asked to elaborate why *IFNL3* types appeared to have limited potential for response-guided treatment strategies[31].

R. According to the comment of the reviewer, the following sentence was added: "Recently it has been demonstrated that although the favorable CC genotype strongly predicted higher rates of on-treatment virological responses and SVR, among patients with RVR, *IFNL3* genotype was associated neither with SVR nor with relapse rates after 24 or 48 weeks[31].

Reviewer (2)

In this review the authors describe the association of *IFNL3* gene polymorphisms with the spontaneous clearance and the outcome of IFN treatment in children. This review discuss the influences of *IFNL3* on IFN therapeutic effects in adults, followed by those in children, providing an excellent review for those who are in charge of pediatric hepatology. However, the reviewer believes that most of readers of the Journal are specialized in adult hepatology, who are not always familiar with child patients infected with HCV.

In this regard, the reviewer would suggest the authors to add another section to this review, focusing on whether IFN-based antiviral therapy should be immediately initiated or not in patients in childhood, based on *IFNL3* SNP status. Recent systematic review (Liver Int 2012:32:258) indicated that few patients had progressive disease in childhood and no clear indication of antiviral therapy. Therefore it could be an option to await antiviral therapy in patients in childhood until introduction of new and more

effective IFN-free regimens.

R. We thank the reviewer for this comment. The section entitled "IFN-BASED TREATMENT IN CHILDREN WITH CHRONIC HEPATITIS C AND SNPS OF *IFNL3* GENE: TO TREAT OR NOT?" was added to the revised manuscript. In this section we commented on the role of IFN-based treatment in children with chronic hepatitis C and on the poor impact of *IFNL3* gene variation alone in predicting the outcome of the treatment. Please note that future research scenarios possibly overcoming this limitation were described in the following and last paragraph of the manuscript. The reference suggested by the reviewer was added.

Reviewer (3)

This manuscript reviewed the current knowledge of association between *IFNL3/IL28B* polymorphisms and hepatitis C infection. However, some concerns need to be clarified before it can be published.

1. It seems that the author just discussed three SNPs (rs12979860, rs8099917, rs12980275) of *IFNL3/IL28B* in the manuscript, and some latest publications were not included. Some but not all of these publications were as following:

(1) Zhang Q, Lapalus M, Asselah T, Laouénan C, Moucari R, Martinot-Peignoux M, Bieche I, Estrabaud E, De Muynck S, Boyer N, Bedossa P, Vidaud M, Marcellin P, Lada O. IFNL3 (IL28B) polymorphism does not predict long-term response to interferon therapy in HBeAg-positive chronic hepatitis B patients. J Viral Hepat. 2013 Oct 10. doi: 10.1111/jvh.12177. [Epub ahead of print]

(2) Prokunina-Olsson L, Muchmore B, Tang W, Pfeiffer RM, Park H, Dickensheets H, Hergott D, Porter-Gill P, Mumy A, Kohaar I, Chen S, Brand N, Tarway M, Liu L, Sheikh F, Astemborski J, Bonkovsky HL, Edlin BR, Howell CD, Morgan TR, Thomas DL, Rehermann B, Donnelly RP, O'Brien TR. A variant upstream of IFNL3 (IL28B) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. Nat Genet. 2013 Feb;45(2):164-71. doi: 10.1038/ng.2521. Epub 2013 Jan 6.

R: The first study suggested by the reviewer is one of the studies published on the correlation between SNPs of *IFNL3* gene and hepatitis B virus infection in adults. We do think that this is an interesting study and an interesting topic but we would prefer not to talk about hepatitis B in adults in this review that focuses on hepatitis C in children. With regard to the second study, as suggested, we did modify the manuscript describing the discovery of IFN-λ4 by Prokunina-Olsson L and collaborators.

2. This reviewer suggests to consider publish this manuscript as a minireview rather than review.

R. This manuscript is an invited review. We think that for its systematic approach to the argument and, according to the comments of the other reviewers that asked to add new paragraphs to the paper, this manuscript could be considered a review. We look forward to know the opinion of the editor.

3. A figure was suggested to add to introduce the mechanism of action of IFNL3, especially for the pathway.

R. Figure 1 was added.

4. Some details of three discussed SNPs need to be added, including location, frequency distribution in different population et al.

R. As suggested by the reviewer 3 and by the reviewer 4 (comment 1) the correct location of the SNPs was described in the paragraph "NOMENCLATURE AND CORRECT DEFINITION OF *IFNL3/IL28B* GENE" (page 3 of the revised manuscript). The frequency distribution of the C allele was reported according to the study of Thomas DL and collaborators [2] in the paragraph "SNPS OF *IFNL3* GENE AND HEPATITIS C IN ADULTS" (page 5 of the revised manuscript).

5. The author also introduced some studies in the adults. These results need to be summarized in a table.

R. The table was added (table 1 of the revised manuscript).

6. This review see no need for Table 1, please remove it.

R. Table 1 was removed and substituted in the revised manuscript by the new table 1 (see comment above).

Reviewer (4)

1.- The authors describe two major SNPs, the rs12979860 and the rs8099917, have been identified on chromosome 19q13.13 near the IFNL3 gene as variants associated with both spontaneous HCV clearance and response to treatment with pegylated-IFN-Î± (Peg-IFN-Î±) combined with ribavirin. However, in the same section the authors describe that early studies failed to find altered mRNA expression of IFNL3 associated with the rs12979860 and the rs8099917 SNPs. Based on the above, it would be important to define the location of the gene that these two polymorphisms are located so they can have an influence on the expression of mRNA

R. As suggested by the reviewer 4 and by the reviewer 3 (comment 4) the correct location of the SNPs was described in the paragraph "NOMENCLATURE AND CORRECT DEFINITION OF IFNL3/IL28B GENE" (page 3 of the revised manuscript).

2.- In the Biology and mechanism of action of type-III IFNS section need to specify which is an unfavorable allele

R: In the revised manuscript we did specify that the T allele is the unfavourable allele.

3.- Is important to integrate the information about the biological effect of the polymorphisms listed

R. In the revised manuscript, the paragraph "BIOLOGY AND MECHANISM OF ACTION OF TYPE-III IFNS" was modified and enriched with more details on the possible mechanism of action of *IFNL3* gene SNPs.

4.- Remove the diagonal (C/C) when involving a genotypes, example (CC)

R. The diagonals have been deleted.

5.- Specify the OR in the text and tables

R. Wherever available and appropriate ORs and 95%CI were reported.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,
Giuseppe Indolfi