

**ESPS Peer-review Report**

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 6369

**Title:** Polymorphisms of IFNL3/IL28B Gene and Hepatitis C: from Adults to Children, Impact on Natural History and on Response to Treatment

**Reviewer code:** 00070847

**Science editor:** Cui, Xue-Mei

**Date sent for review:** 2013-10-16 11:35

**Date reviewed:** 2013-10-19 02:43

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	language polishing	BPG Search:	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

**COMMENTS TO AUTHORS**

Please see minor grammatical edits in the manuscript (attached) and two questions where a brief 1-3 sentence clarification would be useful. This is a well thought through manuscript with useful clinical analysis for the treatment of chronic hepatitis C in children.

**ESPS Peer-review Report**

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 6369

**Title:** Polymorphisms of IFNL3/IL28B Gene and Hepatitis C: from Adults to Children, Impact on Natural History and on Response to Treatment

**Reviewer code:** 00503548

**Science editor:** Cui, Xue-Mei

**Date sent for review:** 2013-10-16 11:35

**Date reviewed:** 2013-10-29 07:47

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input checked="" type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

**COMMENTS TO AUTHORS**

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.

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**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript NO:** 6369

**Title:** Polymorphisms of IFNL3/IL28B Gene and Hepatitis C: from Adults to Children, Impact on Natural History and on Response to Treatment

**Reviewer code:** 00577234

**Science editor:** Cui, Xue-Mei

**Date sent for review:** 2013-10-16 11:35

**Date reviewed:** 2013-11-07 10:45

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	BPG Search:	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> Existed	<input type="checkbox"/> Major revision
		<input type="checkbox"/> No records	

## COMMENTS TO AUTHORS

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. 2. This reviewer suggests to consider publish this manuscript as a minireview rather than review. 3. A figure was suggested to add to introduce the mechanism of action of IFNL3, especially for the pathway. 4. Some details of three discussed SNPs need to be added, including location, frequency distribution in different population et al. 5. The author also introduced some studies in the adults. These results need to be summarized in a table. 6. This review see no need for Table 1, please remove it.

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**ESPS Manuscript NO:** 6369

**Title:** Polymorphisms of IFNL3/IL28B Gene and Hepatitis C: from Adults to Children, Impact on Natural History and on Response to Treatment

**Reviewer code:** 00504393

**Science editor:** Cui, Xue-Mei

**Date sent for review:** 2013-10-16 11:35

**Date reviewed:** 2013-11-12 12:21

CLASSIFICATION	LANGUAGE EVALUATION	RECOMMENDATION	CONCLUSION
<input type="checkbox"/> Grade A (Excellent)	<input type="checkbox"/> Grade A: Priority Publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B (Very good)	<input checked="" type="checkbox"/> Grade B: minor language polishing	<input type="checkbox"/> Existed	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C (Good)	<input type="checkbox"/> Grade C: a great deal of language polishing	<input type="checkbox"/> No records	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D (Fair)	<input type="checkbox"/> Grade D: rejected	<input type="checkbox"/> Existed	<input checked="" type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E (Poor)		<input type="checkbox"/> No records	<input type="checkbox"/> Major revision

## COMMENTS TO AUTHORS

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- $\alpha$  (Peg-IFN- $\alpha$ ) 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 2.- In the "Biology and mechanism of action of type-III IFNs" section need to specify which is an unfavorable allele 3.- Is important to integrate the information about the biological effect of the polymorphisms listed 4.- Remove the diagonal (C/C) when involving a genotypes, example (CC) 5.- Specify the OR in the text and tables