OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
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- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://brief.land/briefland/knowledgebase/category/tree.html#opr.html

Gene, Cell and Tissue
Article DOI: 10.5812/gct.103096
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Peer Review Report for "MicroRNA Prediction in the FVIII Gene Locus: A Step Towards Hemophilia A Control"

Author(s): Halimeh Rezaei, Majid Motovali-Bashi, Sheyda Khalilian

Review Timeline:

Submit Date: 29 Mar 2020
Revised Date: 25 Apr 2020
Accepted Date: 30 Apr 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Nadia Sheibak: Reviewer | **Revision** (0) — 31 Mar 2020

Dear AE,
With respect to the authors, due to lack of novelty, the article is recommended to reject.
Thanks.

Seyed Reza Kazeminezhad: Reviewer | **Revision** (0) — 14 Apr 2020

Dear AE,
Comments for the authors:
- It is better to use (prediction) instead of the word (discovery) in title.
- Please determine which genes are the targets of put-miR1 and put-miR2!
- You can use Miranda, Target Scan/Target Scans, Pictar, Diana-microt, RNA hybrid and Mirwalk software to find miRNA targets.
- Please use mirtronPred tool, that predicts mirtrons from intronic sequences.
- In the reference number 1 it is written (… disorder occurring in 1 in every 5000 male births…) while in the present article it is written (…frequency of one in 5,000 to 10,000 live

births…)!?
- The statistics in text (Based on the natural function of FVIII, Hemophilia A is subcategorized into three various levels: mild (5-25%), moderate (1.5%) and severe (1%), with the prevalence of 50%, 10%, and 40%, respectively) are not available in reference number 2.
Thanks.

Bita Moudi: Associate Editor | **Revision** (0) 15 Apr 2020

Dear EIC,
Reviewers have now commented on this paper. The authors will see that they are advised to revise their manuscript. If they are prepared to undertake the work required, I would be pleased to reconsider my decision.
For their guidance, reviewers' comments are appended below.
If they decide to revise the work, they should submit a list of changes or a rebuttal against each point which is being raised when they submit the revised manuscript.
The revision is due by 25/4/ 2020.
To submit a revision, go to http://genecelltissue.com/en/index.html and log in as an Author. They will see a menu item called Submission Needing Revision. They will find the submission record there.
Yours sincerely
Bita Moudi, PhD
Associate Editor
Gene, Cell and Tissue

Zahra Heidari: EIC | **Revision** (0) 18 Apr 2020

Dear Authors,
Based on the reviewers' and AE comments this manuscript needs major revision and a point-by-point reply to the comments.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Scientific Editor
gene, cell and tissue

Subject: Revision and resubmission of manuscript (ID: 103096)

Dear Editorial Office,

Thank you for your letter and the opportunity to revise our paper on '**microRNA discovery in FVIII Gene Locus: A step towards hemophilia A control**'. We also greatly appreciate the reviewers for their complimentary comments and suggestions that have been immensely helpful.

We have included the reviewer comments immediately after this letter and responded to them, indicating exactly how we addressed each concern or problem and describing the changes we have made. The revisions have been approved by all authors and marked version of the revised manuscript is attached to this message.

We hope the revised manuscript will better suit the Journal.

Sincerely,

Majid Motovali-bashi

Associate professor of Molecular Genetics,

University of Isfahan

Email: mbashi881@gmail.com

Reviewer Comments, Author Responses and Manuscript Changes

- **1**: **It is better to use (prediction) instead of the word (discovery) in title**.

Response: Thank you. We have changed the manuscript title.

- **2**: **Please determine which genes are the targets of put-miR1 and put-miR2!**

Response: Because each of the two proposed sequences is 104 nucleotides long (miRNA precursor), and the exact location of miRNA is not bioinformatically known, it is not possible to identify target genes at this stage. It should be noted that in the laboratory confirmation phase, after designing primer and the exogenous miRNA expression using RT-qPCR, we will be able to determine the miRNA in the proposed sequences and predict its targets.

- **3**: **You can use Miranda, Target Scan/Target Scans, Pictar, Diana-microt, RNA hybrid and Mirwalk software to find miRNA targets.**

Response: Thank you. The proposed databases can find miRNA targets. In this study, a sequence of 104 nucleotides of the miRNA precursor has been identified, which we will be able to introduce after the laboratory confirmation phase (exogenous miRNA expression using RT-qPCR). After the miRNA introduction, we can find our miRNA targets, using these websites.

It should be noted that the databases that we have used in this study, is according to the bioinformatics phase of the following articles*. In fact, the following articles, which include bioinformatics and laboratory confirmation phases, use databases to predict miRNA precursors. Since no article has been found to explain miRNA precursor prediction phase in these articles, we decided to elaborate on the bioinformatics phase of these articles. Certainly, the existence of an article that describes in detail the way in which miRNA precursors are predicted will not be without merit and can form the first phase of a research project. However, in these articles after RT-qPCR, exogenous miRNA expression, cloning and finally miRNA introduction; the miRNAs were introduced to Diana-microt or other tools to predict miR targets. As we said, it is the next step of this study.

* Saleh AJ, Soltani BM, Dokanehiifard S, Medlej A, Tavalaei M, Mowla SJ (2016) Experimental verification of a predicted novel microRNA located in human PIK3CA gene with a potential oncogenic function in colorectal cancer. Tumor Biol 37:14089–14101

* Najafi H, Soltani BM, Dokanehiifard S, Nasiri S, Mowla SJ (2017) Alternative splicing of the OCC-1 gene generates three splice variants and a novel exonic microRNA, which regulate the Wnt signaling pathway. RNA 23:70–85

* Dokanehiifard S, Soltani BM, Parsi S, Hosseini F, Javan M, Mowla SJ (2015) Experimental verification of a conserved intronic microRNA located in the human TrkC gene with a cell type-dependent apoptotic function. Cell Mol Life Sci 72:2613–2625

* Parsi S, Soltani BM, Hosseini E, Tousi SE, Mowla SJ (2012) Experimental verification of a predicted intronic microRNA in human NGFR gene with a potential pro-apoptotic function. PloS ONE 7:e35561

* Hoballa MH, Soltani BM, Mowla SJ, Sheikhpour M, Kay M. Identification of a novel intergenic miRNA located between the human DDC and COBL genes with a potential function in cell cycle arrest. Molecular and cellular biochemistry. 2018 Jul 1;444(1-2):179-86.

* Dokanehiifard S, Yasari A, Najafi H, Jafarzadeh M, Nikkhah M, Mowla SJ, Soltani BM. A novel microRNA located in the TrkC gene regulates the Wnt signaling pathway and is differentially expressed in colorectal cancer specimens. Journal of Biological Chemistry. 2017 May 5;292(18):7566-77.

- **4*: Please use mirtronPred tool, that predicts mirtrons from intronic sequences.**

Response: Thank you for your helpful suggestion, but the databases used in this article are specifically able to identify novel miRNA precursors according to the common characteristics of miRs (such as mentioned articles). One of these features is the cleavage site of the Drosha enzyme, which is not present in mirtrons. In these databases, the cleaved miRNA precursors (by Drosha and Dicer) are introduced as a candidate for the possibility of miRNA presence. Although using mirtronPred tool will definitely be one of our goals in future studies; but, the use of this tool in the present study does not seem appropriate. However, we are still waiting for your valuable comments.

- **5*: In the reference number 1 it is written (… disorder occurring in 1 in every 5000 male births...) while in the present article it is written (…frequency of one in 5,000 to 10,000 live births…)!?**

Response: Thank you. We updated the reference 1 and changed the mentioned sentence which is highlighted in pink.

- **6*: The statistics in text (Based on the natural function of FVIII, Hemophilia A is subcategorized into three various levels: mild (5-25%), moderate (1.5%) and severe (1%), with the prevalence of 50%, 10%, and 40%, respectively) are not available in reference number 2.**

Response: we have checked it and updated the reference 2 and added the reference 3. Thank you. (highlighted in green)

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 26 Apr 2020

Dear AE,
Concerning the manuscript entitled “microRNA prediction in FVIII Gene Locus: A step towards hemophilia A control” for Gene, Cell and Tissue Journal, the authors the F8 gene region to predict novel miRNAs as regulators of the F8 gene and recommended that stem-loop structures can be used as powerful non-invasive biomarkers in early diagnosis of the disease and regulation of factor VIII gene after subsequent experimental verification. The subject of the article is interesting and is recommended to accept in its current version. In addition, the authors have carried out reforms.
Best regards.

REFEREE: Reviewer | **Revision** (1) — 29 Apr 2020

Dear AE,
The author has responded well to all the reviewer comments.
Thanks.

Zahra Heidari: Associate Editor | **Revision** (1) — 30 Apr 2020

Dear EIC,
Rivisions were done well. Thus this manuscript can be accepted for publication in GCT.
Thanks.

Zahra Heidari: EIC | **Revision** (1) — 30 Apr 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.