Name of the journal: World Journal of Nephrology

ESPS manuscript number: 39479

Title: A Unique Interstitial miRNA Signature Drives Fibrosis in a Murine Model of ADPKD.

Authors: Ameya Patil, William E. Sweeney, Jr, Cynthia G. Pan and Ellis D. Avner

Correspondence:

Ameya P. Patil M.D.
Assistant Professor
Department of Pediatrics, Medical College of Wisconsin, Children's Research Institute; Children's' Hospital Health System of Wisconsin; Children's Corporate Center, Suite 510, Mailstop CCC C510
999 North 92nd Street
Wauwatosa, WI 53226
Phone: 414-955-5773
Fax: 414-337-7105
Email: appatil@mcw.edu

Reviewer-1 comments:

I would like to thanks for the opportunity to review the interesting article. In general, the draft had been written well. I have just minor comments for the authors: 1. Cyst volume could be related the renal function progression, beside fibrosis. Are there any correlation between miRNA and the cyst volume of the ADPKD? 2. The study needs positive control with fibrosis tissue, non-ADPKD, to clarify the specified expression of miRNA for the ADPKD fibrosis tissue.

Response-
Thank you for reviewing the manuscript and providing comments.

1) Does cyst volume correlate with GFR decline and miRNA signature?
The data are presented. Until fibrosis proceeds, increased total kidney volume (TKV) correlates with decline in GFR. However, as fibrosis continues, the relationship between TKV and GFR (renal function as measured) is predictably altered. The miRNA signature is correlated with fibrosis and decline in renal function.

2) Should the miRNA signature be compared to another model of fibrosis as a control?
There is no reason to add another model of fibrosis as a positive control-to our knowledge, each (i.e., bilateral 5/6th nephrectomy, unilateral nephrectomy with

partial contralateral nephrectomy, drug-induced damage, etc.) may have its own miRNA signature. There is nothing to be gained by such comparisons, as there is no uniformly-accepted model (a gold standard) of fibrosis.

Reviewer-2 comments:

The manuscript describes the expression of miRNAs using both whole and focal renal tissue (acquired by LCM) in a hypomorphic model of ADPKD. The Introduction, Methods and Conclusions generally well written. The data in the Results are interesting for researchers in the field. Some minor suggestions for the authors to consider: - the description of the Results is very brief and could be improved - some brief justification for the sample size (n=3 at each timepoint) should be provided in the Methods (and if needed, a comment in the Discussion might be useful) - do the authors feel that data from whole kidney of wild-type mice is required? (if needed, a comment in the Discussion might be useful)

3) Why is the n=3?

Average CT values and their standard deviations were reviewed. With little STD DV, the n value is sufficient for appropriate statistical analysis (statement explaining this is included in the manuscript).

4) Why is wild type, normal kidney not used as control?

The appropriate control is pre-fibrotic tissue as presented. The wild type kidney has minimal interstitial tissue that can be targeted for laser capture microdissection. Risk of contaminating the samples with epithelial tissue is high (statement explaining this is included in the manuscript).

The arguments you both have provided to this point are correct.

Response to editor-

1) Add research highlight.

Research highlight is included.

2) Please add PubMed citation numbers and DOI citation to the reference list and list all authors.

References are edited as requested.

Name of the journal: World Journal of Nephrology

ESPS manuscript number: 39479

Title: A Unique Interstitial miRNA Signature Drives Fibrosis in a Murine Model of ADPKD.

Authors: Ameya Patil, William E. Sweeney, Jr, Cynthia G. Pan and Ellis D. Avner

Correspondence:

Ameya P. Patil M.D.
Assistant Professor
Department of Pediatrics, Medical College of Wisconsin, Children's Research Institute; Children's' Hospital Health System of Wisconsin; Children's Corporate Center, Suite 510, Mailstop CCC C510
999 North 92nd Street
Wauwatosa, WI 53226
Phone: 414-955-5773
Fax: 414-337-7105
Email: appatil@mcw.edu

Response to the editor

We would like to take this opportunity to thank the editor and reviewers for their valuable comments, and a thorough and helpful review. We agree that the suggestions have improved the manuscript.
Following corrections were asked on the revision:
(1) The core tip should be less than 100 words.
(2) Please add some subtitles to the results section.

We have revised the core tip. It is now less than 100 words. We have also added subtitles in the result section.