Author’s response to reviews

Title: Differential methylation as a diagnostic biomarker of rare renal diseases: a systematic review

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Author’s response to reviews:

Dear Prof Girish Nadkarni, thank you for taking the time to consider this manuscript. We are pleased to learn our manuscript is potentially acceptably for publication in BMC Nephrology following minor revisions. We have submitted a revised manuscript to BMC Nephrology, alongside a point-by-point response to each point raised describing what amendments have been made.

We hope our revisions in response to the expert editor and reviewers’ comments enable this manuscript to be considered competitive for publication. Please do not hesitate to get in touch if we can provide further information.

Yours sincerely, AJ
Reviewer 1: The manuscript represents systematic review of differential methylation as biomarker for rare renal diseases.

Major points:
1. In Background: it would be worth adding information about differential methylation in health and disease
2. To answer 2nd point of aims and objectives, Authors should describe methylation findings in six diseases listed in discussion
3. In this review only 13 articles were found to describe methylation in rare kidney disease! How can you explain this shortage? And what is clinical impact of these findings?
4. Cancer is affected by epigenetics; did you exclude diseases with kidney tumors?

Minor points:
1. In this study, Can we replace rare renal disease by genetics (inherited) renal disease?
2. In abstract, your search was before Sep 2018 then in eligibility criteria (line 126) your search was before Nov 2017. Can you explain?
3. Did you check methylation websites such as genomeweb, epigenesys or EpiSign for methylation in rare renal disease?

We would like to sincerely thank the reviewer for taking the time to consider our manuscript.

Major points:
1. Whilst methylation in wider health and disease was discussed in the background between lines 97-111, we have now expanded on this, which we hope will help explain the background to this field more fully. Lines 96 – 132 (Background)
2. We agree with the reviewer that to better satisfy our second objective, further elaboration of DNA methylation in the diseases identified would be helpful. We have now included a paragraph on aberrant methylation in IgAN, ADPKD, rare causes of proteinuria and congenital renal agenesis which reflects a more comprehensive discussion of the articles
included in the review. We would also like to confirm this review highlights 5 diseases. Lines 241 - 301 (Discussion)

3. The limited number of studies identified by our highly comprehensive search is indicative of the need to progress studies of differential methylation in rare renal diseases. As discussed in the review, this represents only approximately 5% of all rare renal diseases and is therefore a key research gap. This gap is mostly likely due to the only recent advent of methylation in studies of disease, which has been accelerated in common complex diseases through the use of next generation techniques over the past decade, but which technologies have still largely been unapplied to rare diseases (as is a typical problem for rare diseases across medical advancements). By publishing our article with BMC Nephrology, we hope to raise awareness of this neglected research area and encourage researchers to conduct studies of differential methylation in rare renal disease. The clinical impact of several epigenetic features is described in the text, with ongoing projects such as the recently formed epigenetics sub-domain of the 100,000 genomes project providing strong likelihood of more clinical impact in the near future.

4. Epigenetics and cancer has previously been reviewed, (Morris MR, Latif F. The epigenetic landscape of renal cancer. Nature reviews Nephrology 2017;13(1):47-60. doi: 10.1038/nrneph.2016.168) and as such we chose to consolidate our review to information which is less known to researchers. As well as having previously included the sentence “DNA methylation and renal cancer is reviewed extensively elsewhere”, line 194, reference 31, we have further clarified this in our eligibility criteria, which we hope will satisfy the reviewer’s query. Lines 152 - 153 (Eligibility criteria)

Minor points:

1. We have used the term “rare” disease due to the accepted international definitions of a rare disease rather than an inherited disease. Not all inherited kidney diseases are rare and we would prefer to use the terminology “rare renal disease” to ensure we capture renal conditions that are not inherited in a typical Mendelian pattern.

2. This search was updated in September 2018 to ensure any new articles were captured and that the review was not missing crucial information with the eligible study numbers already so low, this was mistakenly not updated in the eligibility criteria and has now been corrected. Line 148 (Eligibility criteria)

3. We thank the reviewer for pointing us in the direction of these methylation websites and the EpiSign assay, but we did not find any new articles which met the eligibility criteria following searching of these websites. We have included that these websites were
searched, as well as a line about the utility of the EpiSign clinical tool in our background. Lines 122-127 (Background), lines 173-174 (Information sources and search terms) and lines 199 and 200 (results).

Reviewer 2: Given the rare nature of these diseases and the limited research in the area of methylation with respect to these diseases, the authors have given a comprehensive and systematic review. This consolidated information will help researchers identify the thrust area for methylation based research.

We thank the reviewer for taking the time to consider our manuscript and are pleased this reviewer confirms that the information provided will be of help to researchers investigating methylation and rare renal disease.