Author’s response to reviews

Title: Clinical utility of PKD2 mutation testing in a polycystic kidney disease cohort attending a specialist nephrology out-patient clinic.

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Version: 3 Date: 21 May 2012

Author’s response to reviews: see over
Dear Dr. Christopher Morrey,

The BioMed Central Editorial Team

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Re: manuscript Clinical utility of PKD2 mutation testing in a polycystic kidney disease cohort attending a specialist nephrology out-patient clinic by Robinson et al.

Thanks you very much for sending our manuscript for review. The authors greatly appreciate the reviewers for their insightful and constructive comments. I have amended the manuscript accordingly. The changes that have been made are detailed below.

I look forward to receiving your comments.

Yours sincerely
**Reviewer: York Pei**

The authors of this single-centre study report their experience in PKD2 mutation screening in 142 consecutive patients with ADPKD. They found that ~20% of their patients had a pathogenic PKD2 mutation and validated the use of family history of renal disease severity as a cost-effective means to selecting families with mild renal disease for PKD2 screening.

The strengths of this study include:

1. A well-defined prospective cohort of patients without advanced renal failure from a single centre
2. Its report of a higher prevalence of PKD2 using a more population based source is supported by two other recent single centre studies
3. Validation of the use of family history as a means of predicting the underlying gene type (i.e. "a history of one or more older affected family member who developed ESRD or remains renal sufficient at age older than 70" is highly predictive of PKD2)

Notwithstanding these strengths, there are also several issues that the authors need to address:

1. **Their observation of 25.9 and 35.6 % of the probands without and with PKD2 mutations did not have a family history represents a very high rate compared to other series. They should expand on their discussion on why their observation appears to be discordant with the published series.**

   The family history was collected from each proband at their recruitment clinic visit. The figures for those without a family history are therefore self reported data and represent those individuals who had no knowledge of the condition within their family. This was before any additional family screening was carried out based on their diagnosis. We would therefore expect that with family screening these figures would appear similar to other studies where no other affected family members were identified following screening. The discussion has been extended to address this point.

2. **They should differentiate between single-centre vs. multiple centre studies in Table 1. Only single centre studies can provide results that estimates population prevalences of PKD1 and PKD2.**

   This has been amended.

3. **They should perform post-hoc sample size calculations which would likely show that the reason for a lack of differences in the three CKD stages between patients with the two gene mutation types is related to power.**

   Post hoc power calculations have been performed and confirm the study is underpowered to detect these differences. This has been included in the discussion to inform future studies and support the need for large well characterized cohorts.

4. **Figure 3 is not really very useful and should be deleted.**

   We agree that Figure 3A contributes little to demonstrating the variability in eGFR values over time. However 3B and 3C we feel illustrates well the variability in decline in renal function in individuals and as a group based on the genotype data. In particular 3B demonstrates how some individuals decline much more rapidly than others and this is more easily appreciated with the use of colour. Figure 3 could be added to supplementary data if required.
(5) There is an inconsistency in their recommendation that PKD2 mutation screening should be offered to all ADPKD patients except those whose family members developed ESRD under age 50 (line 9 from top of page 14) and whose family members developed ESRD before the sixth decade (lines 1 and 2 from the bottom of page 14).
Under age 50 and before the sixth decade state the same thing. However for clarity a single consistent statement has been used.

(6) They should update their references on PKD1 hypomorphic alleles as a potential cause of mild renal disease.
This has been done.

Reviewer: Carsten Bergmann
Robinson and colleagues report mutation analysis of PKD2 in a clinically well-evaluated cohort of 142 patients with ADPKD and CDK stage 4 or less. Overall, this is a well-done study. Although ADPKD mutation analysis is incomplete and most aspects and results have been already discussed in the literature, studies like this are important and worth publishing. However, there are a few points that the authors are recommended to address and which may make the paper more robust.
1. While there is no doubt on the usually milder clinical course of PKD2 compared to PKD1, the authors are asked to shortly comment on cases with early and severe disease manifestation.
This has been included in the discussion.

2. Page 7, 1st paragraph, balanced translocation: Please spend a few more words on the family history etc.
Further information has been provided.

3. Page 8, 1st paragraph: Please explain if also for these different (sub)cohorts age and other parameters were comparable?
The small size of the PKD2 group makes further subgroup analysis by age and gender uninformative. This has been addressed in the hazard modeling of the rate of progression to CKD3 for example where larger groups sizes are required.

4. Page 10, 3rd paragraph, “not aware of a FH of ADPKD”: Please also discuss here other ways of inheritance and that PKD genetics becomes more complex.
Further discussion has been included based on other reviewer’s comments as well.

5. Overall, some statements should be more carefully (e.g., “patients with a FH of ESRF before age 50 can be excluded from PKD2 testing”).
These sentences have been revised in the context of the revised manuscript.

Reviewer's report
Title: Clinical utility of PKD2 mutation testing in a polycystic kidney disease cohort attending a specialist nephrology out-patient clinic.
Version: 2 Date: 20 March 2012
Reviewer: Curie Ahn
Reviewer's report:
• Major Compulsory Revisions

1) Although it is a good idea to screen PKD2 mutation in the suspected ADPKD patients, the predictive value of FH of ESRF seems more economical way to clinically predict patients’ outcome. You should clarify this point in your discussion.

This point has been addressed although some individuals with no PKD2 mutation also had a mild FH ie the test had good PPV but low sensitivity. Therefore the FH only guides who should be tested and is not a replacement for testing except in those with a FH of ESRF before age 50 yrs.

2) What is the novel finding of your study? We already know patients with PKD2 mutation have slow disease progression and low number of cysts. You should clarify the strength of your study in your discussion section.

The novelty of the study is to apply PKD2 gene testing and a FH questionnaire to a well defined population of patients attending a routine nephrology out-patient clinic. This is indeed where most cases are followed up and represents a population that has not previously been studied in detail using these methods. Most studies have focused on cohorts with large families suitable for linkage analysis or including those who have already developed ESRF. Therefore we have included individuals with no FH and preserved renal function in our analysis.

3) The aim of this study was to identify factors that can be used to offer targeted gene testing and to provide patients with improved prognostic information. You concluded that PKD2 mutation testing can be useful to all but those whose relatives have developed ESRF before the sixth decade. However, even without PKD2 mutation analysis, we already know from the previous study that patients with FH of ESRF <50 more likely to have PKD1 mutation and FH of ESRF >70 more likely to have PKD2 mutation. What is the additional role of PKD2 mutation analysis?

PKD2 mutation analysis was required to analyse and assess the role of the FH. Our result confirms the previously published study of FH data. However the PPV and NPV are not 100% sensitive or specific and so PKD2 testing is still required except in the one group with ESRF before age 50 years. Our recommendation is to exclude individuals with a FH or ESRD <50 yrs from molecular analysis using PKD2 testing. This point has been clarified.

• Minor Essential Revision

1) In the method section, it is better to describe the median or mean follow-up duration of your cohort.

Individuals in the cohort under study were referred sequentially to the clinic between 2005 and 2009 and data analysed in 2011. The median and range have therefore been provided.

2) It is better to mention the limitation of your study (small number of patients, retrospective study, etc.) in the discussion section.

This has been amended in the discussion. The study is however prospective.

3) Figure legends should describe the contents of the figures. Please add the description of each figure in your figure legends.

This has been amended.

4) There are some typos in the title of tables. Please recheck they have the same format ‘Table O. Title.’ For example, Supplementary Table 1 has description rather than the title. Supplementary Table 2 does not have the title.

These has been amended.