Author's response to reviews

Title: The Clinical Significance of Aldosterone Synthase Deficiency: Report of a Novel Mutation in the CYP11B2 gene

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Responses to reviewers

Reviewer 1
Reviewer: Peter Igaz
Reviewer's report:
As a minor discretionary revision, I would propose to the authors to include a figure on the 3-dimensional modelling and potential consequence of the mutation.
A: Thank you for the suggestion. We have added a figure of the 3-D model of the mutant with the novel mutation, including a legend on the potential consequence of the mutation (Figure 2).

Reviewer 2
Reviewer: Elise P Gomez-Sanchez
Reviewer's report:
1) Suggested changes for syntax:
Abstract: “...facilitate clinical management of the patient and ASSESSMENT OF the genetic implication in their offspring”
Last sentence of discussion: “NEITHER mutation WAS detected in the patient’s brother.”
A: Thank you for your comments. These have been amended as suggested (lines 28-29 and line 101).
2) 4th paragraph of the conclusions: Only indapamide? Or any thiazide or thiazide-like diuretic?
Please clarify these 2 sentences. Was this the same patient?

“Generalised weakness with marked hyperkalaemia and dehydration after institution of indapamide for hypertension and bowel preparation for barium enema has been reported as the first presentation in a middle-aged man[13]. Interestingly, past history revealed vomiting and failure to thrive in early infancy that resolved without any mineralocorticoid replacement[13].”

A: The 2 sentences referred to the same patient and have been amended, as suggested, to, “Generalised weakness with marked hyperkalaemia and dehydration has been reported as the first presentation in a middle-aged man after concurrent institution of indapamide for hypertension and bowel preparation for barium enema. Interestingly, further questioning revealed a past history of vomiting and failure to thrive in early infancy that resolved without any mineralocorticoid replacement[13].” (lines 133 – 138).

Only indapamide, a thiazide-like diuretic, has been used.

3) This still happens, so should be in present tense:

“It has been shown that mineralocorticoid receptor expression in human kidneys began with low levels in late gestation and rose progressively after birth[14]”

A: This has been amended as suggested. “Began” has been replaced with “begins” and “rose” with “rises” (lines 141 – 142).

Reviewer 3
Reviewer’s report
Reviewer: Michael Stowasser
Reviewer’s report:
This is a well written paper describing a novel mutation in CYP11B2 causing aldosterone synthase deficiency. The following comments are minor and mostly discretionary only and aimed at improving the paper.
1. Page 2 - The background section of the Abstract is rather long and could be shortened. Suggest delete the first sentence as it is rather common knowledge.
   Thank you for your comments. The first sentence has been deleted as suggested.
2. Page 2, line 12 – suggest insert “Chinese” after “33-year old”.
   Thank you for your comments. This has been amended as suggested (line 30).
3. Page 2, line 17 – suggest insert “CYP11B2” after “novel”.
   This has been amended as suggested (line 35).
4. Page 2, lines 22-24 – suggest reword to “Although a rare cause of hyperreninaemic hypoaldosteronism, aldosterone synthase deficiency should be suspected and the diagnosis sought in patients who present with life-threatening salt-wasting in infancy, as it has a good ... etc”.
   This has been reworded in line 40 - 43.
5. Page 4, line 2 – suggest replace “electrolyte” with “sodium” to be more
specific.
This has been amended as suggested (line 51).

6. Page 4, lines 5 and 6 – as small amounts of CYP11B2 expression have been reported in tissues other than the adrenal cortex, suggest reword to “It is synthesized by aldosterone synthase, an enzyme encoded by CYP11B2, expression of which is almost entirely confined to the adrenal cortex and exclusively in the zona glomerulosa layer.”
Thank you for the suggestion, reworded as suggested (lines 53 – 56).

7. Page 4, line 15 – suggest insert “individuals” after “Indian”.
This has been amended as suggested (line 65).

The sentence has been changed (line 66 - 68).

9. Page 4, line 28 – insert “at the time of this report” after “The index patient, “.
This has been amended as suggested (line 72).

10. Page 5, line 2 – change “has” to “had”.
"Has” was changed to “had” in line 76.

11. Page 5, line 13 – insert “years” after “33”.
This has been amended as suggested (line 88).

12. Page 6, line 7 – insert “in whom” after “hyperreninaemic hypoaldosteronism, and “.
This has been amended as suggested (line 105).

13. Page 6, line 17 – replace “until further evaluation with” with “pending”.
This has been amended as suggested (line 115).

14. Page 7, line 3 – insert “and” after “of 18OHB, “.
This has been amended as suggested (line 122).

15. Page 7, line 22 – replace “began” with “begins” and in line 23 replace “rose” with “rises”.
Thank you. “Began” has been replaced with “begins” and “rose” with “rises” (line 142).

16. Page 8, line 1 – delete “the” and in line 2 change “more” to “greater”.
“The” has been deleted and “more” changed to “greater” (line 143).

17. Page 8, line 5 – insert “therefore” after “may”.
This has been amended as suggested (line 148).

18. Page 9, line 9 – insert “the” before “secondary structure”.
“the” has been inserted before “secondary structure” (line 175).

19. Page 9, line 12 – “and” after “activity (16.3%), “.
“and” has been added after “activity (16.3%), “ (line 178).

Editorial requirements

1) There was no funding body for acquiring/analysing the data or preparing the manuscript, as all the tests were performed as part of the patient care. Therefore, we have not included an Acknowledgements section to our manuscript.

2) The initial heading for “conclusion” has been changed to “discussion” (line 103). New heading for “conclusion” has been added to line 180, with minor amendment to the last sentence, to “Our case illustrates the clinical significance to recognize this condition as it has a good long-term prognosis when adequate fludrocortisone replacement is instituted.”

3) Line and page numbers have been inserted to the main text of the manuscript.