Reviewer's report

Title: Autosomal dominant pseudohypoaldosteronism type 1 with a novel splice site mutation in MR gene

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Reviewer: Maria-Christina Zennaro

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The paper by Kanda et al is interesting in that it shows for the first time analysis of mRNA from urinary sediments in patients with PHA1, showing that the wild type and mutant mRNA coexist in target tissue. However, in the absence of protein studies and functional analyses of the truncated receptor, no clear statement can be done on the pathogenic mechanism of PHA.

Major compulsory revisions:

Introduction: the authors should also distinguish PHA1 according to the clinical feature of renal or generalized mineralocorticoid resistance, according to Hanukoglu et al, J Clin Endocrinol Metab 1991. Also, they should correct, introduction, line 6: ‘patients with renal, autosomal dominant PHA1………….’.

Introduction, second paragraph, line 7; please correct: ‘conserved DNA binding domain enocoded by exon 3-4 and a ligand binding domain responsible for ligand binding and ligand-dependent transactivation encoded by exons 5-9

Discussion:

Page 6: the references concerning the cited work of Sartorato et al are missing.

Discretionary Revisions:

Page 7: Concerning the suggestion that there might be incomplete NMD in the patients’ tissues, it is remarkable that the authors had to use nested PCR and 35 cycles of amplification to detect the exon-skipped mRNA. Is this also true for the mRNA deriving from the wild type allele? It would be certainly relevant to perform qPCR in order to determine the ratio of one transcript vs the other.

A complete characterization of the underlying mechanism would of course require detection of the truncated protein in vivo and functional analysis in vitro. Without this information, one has to hypothesize that, although not mediated by NMD, haploinsufficiency given to the loss of major functional domains of the receptor, is the pathogenic mechanism of PHA1 in this patient.

Conclusions

Genotype-phenotype correlations are very difficult in PHA1 patients, given the highly variable phenotypic expression. However, the authors should consider that salt intake in the diet may modulate the phenotype after weaning and that some
patients may compensate their phenotype without treatment just by a high salt diet.

Minor:
The manuscript needs some English editing.
Introduction, line 9: please correct: ‘In most cases, renal PHA1 is the........’
Methods, DNA amplification: Please correct: ‘all eight coding exons…’
Results: Only the mutation nomenclature according to the guidelines of the Human Genome Variation Society should be indicated; authors please delete (IVS 6-2 A>C).
Fig. 1: please correct mutation nomenclature
Abbreviations: plasma renin activity

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
I declare that I have no competing interests