Reviewer's report

Title: A Young Child with Pseudohypoaldosteronism Type II by a Novel Mutation of Cullin 3.

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Reviewer: Thimo Kurz

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In this manuscript the authors describe the case of a three-year old girl who was diagnosed with PHA II. To elucidate the molecular cause of the disease the authors searched for known disease-causing mutations in the genome of the individual. They identified that the patient carries a mutation in the CUL3 gene, which results in the improper splicing of exon 9. Such exon 9 splice mutations have recently been reported independently by the Lifton as a genetic cause of PHA II that is distinct from known mutations in the WNK1 and WNK4 kinases.

The authors now describe a young patient with a similar mutation than previously described, and as such independently confirm the previous findings. The analysis is done properly and the conclusions are sound, however, the results are not terribly surprising as such, as mutations in CUL3, which cause PHA II, are now well-established.

What is most interesting in this report is the young age of diagnosis and the relative severity of the disease at age 3. It would have been beneficial had the authors discussed this observation further, as it is rather unusual and reconfirms the notion that CUL3 mutations may be much more severe than other known mutations that cause PHA II.

Nevertheless, the report is of interest and I can recommend publication if some points are addressed:

Compulsary Revisions:

1. In the title the authors call the identified mutation in the patient “novel”. However, this term is rather vague and should generally be avoided. If they want to adhere to using it, they should better explain what they mean with a “novel” mutation. Is it that the identified mutation has not been identified in other patients before? If so, they need to discuss this fact and put it into relation to known mutations in CUL3 that cause PHAII. Where is the mutation located? What residue is affected and where is the affected residue relative to known mutations in CUL3? From what I can see, it appears as if the reported mutation lies in the Intron 9 splice donor site, which has been reported to be mutated by the Lifton group (PMID:22266938). The authors need to discuss this fact and explain why they consider the identified mutation a novel mutation.

2. Next, the authors conclude that the mutation in the patient is a de novo
mutation, as they cannot find the same mutation in the mother or brother of the patient. However, there is no mention of the sequencing of (confirmed) paternal DNA. As these are dominant mutations, there is no way of telling if this is a de novo mutation or a paternally inherited mutation. The authors need to clarify why they think it is de novo or remove this statement.

Minor Essential Revisions:

3. In the first paragraph of the conclusions the authors reference their own work that suggests that WNK4 is a substrate of CUL3/KLHL3 and that mutations in CUL3 and KLHL3 exert their pathogenic effect by a lack of WNK4 ubiquitylation/degradation. While this reference is correct, the paper cited was not the first one to report this finding, which instead was a paper by Ohta et al. in the Biochemical Journal (PMID: 23387299). Furthermore, shortly afterwards the Lifton group reported the same finding in PNAS (PMID: 23576762), both these papers should also be cited to accurately reflect the literature.

4. There are typographical and grammatical errors throughout the document. The authors should take the time to carefully read the manuscript and correct any mistakes.

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

Quality of written English: Needs some language corrections before being published

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 financial interest