Reviewer's report

Title: Exome sequencing identifies a deletion in PIK3R1, causing a severe form of SHORT syndrome

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Reviewer: david Dyment

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The authors report 2 cases of SHORT syndrome. One case has the recurrent c.1945C>T mutation and the other has a novel c.1929_1933delTGGCA mutation. The cases are well described and 1 of the mutations is novel. There are no functional studies performed.

My comments fall into the minor but essential category.

1. The writing at time is awkward. For example, the first sentence reads, “Rare syndromes are genetic disorders that affect a reduced number of individuals in the world”. Firstly, a rare syndrome does not have to be genetic. Also by stating “rare”, the frequency, by definition, is low. If you add all the rare syndromes together, there are actually a great number of individuals worldwide affected with rare disease. I would stress a rewrite of this sentence and other sentences that are similar.

2. I would strike “severe” from the title. The patient has SHORT and seems similar to other published cases (for example, see Chudasama et al; family 1).

3. I would edit/delete the conclusion at the end of the second paragraph, ie “...we conclude that this deletion causes the development of a severe form of SHORT syndrome...”. There are other cases reported with a truncated protein and the phenotype in these cases has not been noted to be dissimilar to those cases with the recurrent missense mutation. The inference that there is a genotype:phenotype correlation is premature and would need a meta-analysis of all known cases to be performed versus the 1 case reported here. As mentioned, I am not convinced that this case is any more severe than other published cases.

4. The authors state several times, “in preparation of the manuscript” other studies were published. I do not think they have to repeat this as it may actually be doing the group a disservice. The 3 AJHG papers were published in July of 2013 and 8 months have now passed and another 4th paper published by Schroeder et al., 2013.

If they must, I would strongly suggest that they state this 1x in the Material and Methods as it does speak to their choice of sequencing technology.

5. The authors should cite the 4th paper by Schroeder et al., especially given the presence of the pulmonary stenosis.

6. I would like to know how Patient1 is being treated for their diabetes, ie how
severe is his insulin resistance.

7. How was Pt2 assessed for insulin resistance at 6 months of age, and what were the lab values (if any).

Thank you for the opportunity to review this manuscript.

**Level of interest:** An article of importance in its field

**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 interests'